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(57) Abstract

A novel plant gene is provided, which is a member of the *mdr* family of genes encoding ABC transporters. The gene is inducible by NPPB, and is preferentially expressed in roots upon induction. The gene is useful for detoxification of certain xenobiotics to protect plants from the detrimental effects of such compounds. Also provided are plants that over–express and under–express this *mdr* gene.

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XENOBIOTIC DETOXIFICATION GENE FROM PLANTS

This application claims priority to U.S. 60/101,814, filed September 25, 1998, the entirety of which is incorporated by reference herein.

Pursuant to 35 U.S.C. §202(c), it is acknowledged that the U.S. Government has certain rights in the invention described herein, which was made in part with funds from the National Science Foundation, Grant No. IBN-9416016.

FIELD OF THE INVENTION

This invention relates to the field of stress resistance in plants. In particular, the invention provides a novel gene from plants, which encodes an MDR-like ABC transporter, involved in detoxification of certain xenobiotics to protect plants from their detrimental effects.

BACKGROUND OF THE INVENTION

Several publications are referenced in this application to describe the state of the art to which the invention pertains. Each of these publications is incorporated by reference herein.

Environmental stress is one of the most important limitations on plant productivity, growth and survival. An ever-increasing source of environmental stress to plants is the stress caused by environmental pollutants in the soil, water and atmosphere. Such pollutants include herbicides, pesticides and related agronomic products, as well as organic and inorganic waste material from industry and other sources. Other toxic agents that threaten the survival of plants include various toxins produced by ephiphytic or soilborne

microorganisms, such as fungi and bacteria.

In order to survive in toxic environments, plants must have mechanisms to detoxify xenobiotics, heavy metals and other toxic compounds. This generally involves modification of the toxic compound and subsequent excretion into the vacuole or apoplastic space. Recently, certain ATP-binding cassette (ABC) transporters have been identified in plants, which appear to be involved in the detoxification process.

The ABC transporter family is very large, with representatives existing in many different classes of organisms. Two well studied groups of ABC transporters, encoded by *mdr* and *mrp* genes, respectively, are associated with the multi-drug resistance phenomenon observed in mammalian tumor cells. The *mdr* genes encode a family of P-glycoproteins that mediate the energy-dependent efflux of certain lipophilic drugs from cells. The *mrp* genes encode a family of transporters that mediate the extrusion of a variety of organic compounds after their conjugation with glutathione. *YCF1*, the yeast homolog of *mrp*, encodes a protein capable of glutathione-mediated detoxification of heavy metals.

Homologs of *mrp* and *mdr* genes have been identified in plant species. In *Arabidopsis thaliana*, the glutathione-conjugate transporter encoded by the *mrp* homolog is located in the vacuolar membrane and is responsible for sequestration of xenobiotics in the central vacuole (Tommasini et al., FEBS Lett. 411: 206-210, 1997; Li et al., Plant Physiol. 107: 1257-1268, 1995). An *mdr*-like gene (*atpgp1*) has also been identified in *A. thaliana*, which encodes a putative P-glycoprotein homolog. The *atpgp1* gene was found to share significant sequence homology and structural organization with human *mdr* genes, and was expressed with particular

abundance in inflorescence axes (Dudler & Hertig, J. Biol. Chem. 267: 5882-5888, 1992). Other MDR homologs have been found in potato (Wang et al., Plant Mol. Biol. 31: 683, 1996) and barley (Davies et al., Gene 199: 195, 1997).

The aforementioned *mrp* and *mdr* plant homologs were identified as a result of an effort to understand the molecular basis for development in plants of cross-resistance to herbicides of unrelated classes. However, these transporters are likely to serve the more general role in plants of sequestering, secreting, or otherwise detoxifying various organic and inorganic xenobiotics. Accordingly, it will constitute an advance in the art of plant genetic engineering of stress tolerance to identify and characterize other members of this class of transporters in plants.

SUMMARY OF THE INVENTION

In accordance with the present invention, a new plant *mdr* homolog has been identified. Unlike the previously identified plant *mdr* homologs, this new gene is inducible by a class of compounds known to inhibit chloride ion channels.

According to one aspect of the invention, a nucleic acid isolated from a plant is provided, which encodes a p-glycoprotein that is inducible by exposure of the plant to NPPB. The isolated nucleic acid is preferentially expressed in plant roots upon exposure of the plant to NPPB. In a preferred embodiment, the plant from which the nucleic acid is isolated is selected from the group consisting of *Brassica napus* and *Arabidopsis thaliana* and is 3850-4150 nucleotides in length. In a more preferred embodiment, the nucleic acid has the restriction sites shown in Figure 4 for at least three

restriction enzymes. In particularly preferred embodiments, the nucleic acid molecule encodes a polypeptide having SEQ ID NO:2. In an exemplary embodiment, the nucleic acid is a cDNA comprising the coding region of SEQ ID NO:1 or SEQ ID NO:10.

According to another aspect of the invention is an expression cassette that comprises a plPAC gene operably linked to a promoter, and in a more preferred embodiment the plPAC gene is from *Arabidopsis*. In preferred embodiments, the expression cassette comprises the cauliflower mosaic virus 35S promoter, and part of all of SEQ ID NO:1 or SEQ ID NO:10. Further included in this aspect is a vector comprising the expression cassette and a method for producing transgenic plants with the expression cassette and vector.

Another aspect of the invention are transgenic cells and plants containing the nucleic acids of the invention. In one preferred embodiment, the nucleic acids are be in the aforementioned expression cassette. Furhter included in this aspect are reporductive units from the transgenic plant.

According to another aspect of the invention, an isolated nucleic acid molecule is provided, which has a sequence selected from the group consisting of: a) SEQ ID NO:1 and SEQ ID NO:10; b) a nucleic acid sequence that is at least about 60% homologous to the coding regions of SEQ ID NO:1 or SEQ ID NO:10; c) a sequence hybridizing with SEQ ID NO:1 or SEQ ID NO:10 at moderate stringency; d) a sequence encoding part or all of a polypeptide having SEQ ID NO:2; e) a sequence encoding an amino acid sequence that is at least about 70% identical to SEQ ID NO:2; f) a sequence encoding an amino acid sequence that is at least about 80% similar to SEQ ID NO:2; g) a sequence encoding an amino acid sequence that

is at least about 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and h) a sequence hybridizing at moderate stringency to a sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2. A polypeptide produced by expression of the above listed sequences is also provided.

According to another aspect of the invention, an isolated plant p-glycoprotein, which is inducible upon exposure of the plant to NPPB, is provided. The polypeptide preferably confers upon a cell in which it is found resistance to Rhodamine 6G. The polypeptide is preferentially produced in roots upon the exposure to the NPPB. The polypeptide is preferrably from *Brassica napus* or *Arabidopsis thaliana*. In most preferred embodiments, the polypeptide has a sequence that is a) an amino acid sequence that is at least 80% similar to SEQ ID NO:2; b) an amino acid sequence that is at least 70% identical to SEQ ID NO:2; c) an amino acid sequence that is at least 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and d) an amino acid sequence encoded by a nucleic acid sequence hybridizing at moderate stringency to a amino acid sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

According to other aspects of the invention, antibodies immunologically specific for the polypeptides of the invention are provided, that immunologically specific to any of the polypeptides, of polypeptide encoded by the nucleic acids of the invention. In a preferred embodiment, the antibody is immunospecific to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

According to another aspect of the invention, a plant p-glycoprotein gene promoter, which is inducible by NPPB, is also provided. In a preferred embodiment, the promoter is part or all of residues 1-3429 of SEQ ID

NO:10.

According to another aspect of the invention, plants that have reduces levels of plPAC protein are provided. In a preferred embodiment, these plants have mutations in the *plPAC* gene, and in a particularly preferred embodiment, the *plPAC* gene is mutated due to the insertion of a T-DNA. Also provided with this aspect is a method for selecting plants with mutations in *plPAC* using SEQ ID NOS:11-14 as PCR primers.

These and other features and advantages of the present invention will be described in greater detail in the description and examples set forth below.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Amino acid sequence lineup of *ATPAC* deduced amino acid sequence and the amino acid sequences of related mammalian and plant genes. The lineup shows the ATPAC deduced amino acid sequence (SEQ ID NO:2) compared with (1) hmdr1 (SEQ ID NO:3); (2) mmdr1 (SEQ ID NO: 4); (3) hmdr3 (SEQ ID NO:5); (4) mmdr2 (SEQ ID NO:6); (5) atpgp1 (SEQ ID NO:7); and (6) atpgp2 (SEQ ID NO:8). A consensus sequence (SEQ ID NO: 9) is also shown.

Figure 2. Graph depicting the effect of rhodamine 6G on the growth rate of cells transformed with and expressing *ATPAC* as compared with control cells not containing *ATPAC*.

Figure 3. Restriction map of genomic clone of *ATPAC*, SEQ ID NO:10.

Figure 4. Restriction map of cDNA clone of *ATPAC*, SEQ ID NO:1.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

Various terms relating to the biological

molecules of the present invention are used hereinabove and also throughout the specification and claims.

With reference to nucleic acids of the invention, the term "isolated nucleic acid" is sometimes used. This term, when applied to DNA, refers to a DNA molecule that is separated from sequences with which it is immediately contiguous (in the 5' and 3' directions) in the naturally occurring genome of the organism from which it was derived. For example, the "isolated nucleic acid" may comprise a DNA molecule inserted into a vector, such as a plasmid or virus vector, or integrated into the genomic DNA of a procaryote or eucaryote. An "isolated nucleic acid molecule" may also comprise a cDNA molecule.

With respect to RNA molecules of the invention the term "isolated nucleic acid" primarily refers to an RNA molecule encoded by an isolated DNA molecule as defined above. Alternatively, the term may refer to an RNA molecule that has been sufficiently separated from RNA molecules with which it would be associated in its natural state (i.e., in cells or tissues), such that it exists in a "substantially pure" form (the term "substantially pure" is defined below).

Nucleic acid sequences and amino acid sequences can be compared using computer programs that align the similar sequences of the nucleic or amino acids thus define the differences. For purposes of this invention, the DNAStar program (DNAStar, Inc., Madison, Wisconsin) and the default parameters used by that program are the parameters intended to be used herein to compare sequence identity and similarity. Alternately, the Blastn and Blastp 2.0 programs provided by the National Center for Biotechnology Information (at http://www.ncbi.nlm.nih.gov/blast/ ; Altschul et al., 1990, J Mol Biol 215:403-410) using a gapped alignment

with default parameters, may be used to determine the level of identity and similarity between nucleic acid sequences and amino acid sequences.

The term "substantially the same" refers to nucleic acid or amino acid sequences having sequence variation that do not materially affect the nature of the protein (i.e. the structure, thermostability characteristics and/or biological activity of the protein). With particular reference to nucleic acid sequences, the term "substantially the same" is intended to refer to the coding region and to conserved sequences governing expression, and refers primarily to degenerate codons encoding the same amino acid, or alternate codons encoding conservative substitute amino acids in the encoded polypeptide. With reference to amino acid sequences, the term "substantially the same" refers generally to conservative substitutions and/or variations in regions of the polypeptide not involved in determination of structure or function.

The terms "percent identical" and "percent similar" are also used herein in comparisons among amino acid and nucleic acid sequences. When referring to amino acid sequences, "percent identical" refers to the percent of the amino acids of the subject amino acid sequence that have been matched to identical amino acids in the compared amino acid sequence by a sequence analysis program. "Percent similar" refers to the percent of the amino acids of the subject amino acid sequence that have been matched to identical or conserved amino acids. Conserved amino acids are those which differ in structure but are similar in physical properties such that the exchange of one for another would not appreciably change the tertiary structure of the resulting protein. Conservative substitutions are defined in Taylor (1986,

J. Theor. Biol. 119:205). When referring to nucleic acid molecules, "percent identical" refers to the percent of the nucleotides of the subject nucleic acid sequence that have been matched to identical nucleotides by a sequence analysis program.

With respect to protein, the term "isolated protein" or "isolated and purified protein" is sometimes used herein. This term refers primarily to a protein produced by expression of an isolated nucleic acid molecule of the invention. Alternatively, this term may refer to a protein which has been sufficiently separated from other proteins with which it would naturally be associated, so as to exist in "substantially pure" form.

The term "substantially pure" refers to a preparation comprising at least 50-60% by weight the compound of interest (e.g., nucleic acid, oligonucleotide, protein, etc.). More preferably, the preparation comprises at least 75% by weight, and most preferably 90-99% by weight, the compound of interest. Purity is measured by methods appropriate for the compound of interest (e.g. chromatographic methods, agarose or polyacrylamide gel electrophoresis, HPLC analysis, and the like).

With respect to antibodies of the invention, the term "immunologically specific" refers to antibodies that bind to one or more epitopes of a protein of interest, but which do not substantially recognize and bind other molecules in a sample containing a mixed population of antigenic biological molecules.

With respect to oligonucleotides, the term "specifically hybridizing" refers to the association between two single-stranded nucleotide molecules of sufficiently complementary sequence to permit such hybridization under pre-determined conditions generally

used in the art (sometimes termed "substantially complementary"). In particular, the term refers to hybridization of an oligonucleotide with a substantially complementary sequence contained within a single-stranded DNA or RNA molecule of the invention, to the substantial exclusion of hybridization of the oligonucleotide with single-stranded nucleic acids of non-complementary sequence.

The term "expression cassette", as used herein, comprises 5' and 3' regulatory regions operably linked to a coding sequence. The coding sequence may be in the sense or antisense orientation with respect to the 5' regulatory region.

The term "promoter region" refers to the 5' regulatory regions of a gene.

The term "reporter gene" refers to genetic sequences which may be operably linked to a promoter region forming a transgene, such that expression of the reporter gene coding region is regulated by the promoter and expression of the transgene is readily assayed.

The term "selectable marker gene" refers to a gene product that when expressed confers a selectable phenotype, such as antibiotic resistance, on a transformed cell or plant.

The term "operably linked" means that the regulatory sequences necessary for expression of the coding sequence are placed in the DNA molecule in the appropriate positions relative to the coding sequence so as to effect expression of the coding sequence. This same definition is sometimes applied to the arrangement of coding sequences and transcription control elements (e.g. promoters, enhancers, and termination elements) in an expression vector.

The term "DNA construct" refers to genetic

sequence used to transform plants and generate progeny transgenic plants. These constructs may be administered to plants in a viral or plasmid vector. Other methods of delivery such as Agrobacterium T-DNA mediated transformation and transformation using the biolistic process are also contemplated to be within the scope of the present invention. The transforming DNA may be prepared according to standard protocols such as those set forth in "Current Protocols in Molecular Biology", eds. Frederick M. Ausubel et al., John Wiley & Sons, 1995.

The term "xenobiotic" refers to foreign chemicals or agents not produced or naturally found in the organism. The term is commonly used in reference to toxic or otherwise detrimental foreign chemicals, such as organic pollutants or heavy metals.

II. Description of *plPAC* and its Encoded Polyeptide

In accordance with the present invention, a nucleic acid encoding a novel ATP-binding-cassette (ABC) transporter has been isolated and cloned from plants. The nucleic acid is referred to herein as *plPAC*.

A cDNA clone of the *plPAC* from *Arabidopsis thaliana*, an exemplary *plPAC* of the invention, is described in detail herein and its nucleotide sequence is set forth in Example 1 as SEQ ID NO:1. This nucleic acid molecule is referred to as "*ATPAC*". It is 36% identical and 51% similar to human *mdr1* across the entire sequence. It is 51% identical to the *atpgp1* gene reported by Dudler & Hertig (1997, *supra*) and 50% identical to *atpgp2*, a close homolog of *atpgp1*, published in the Genbank database. ATPAC protein is 65% similar to atpgp1 and atpgp2 proteins.

A partial clone of a *plPAC* of the invention was originally isolated from *Brassica napus* via differential expression screening of plants grown in the presence or absence of the chloride channel blocker, 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). A 0.5 kb gene fragment was identified, which had been up-regulated in response to NPPB treatment. This cDNA fragment was used to screen an *Arabidopsis* cDNA library, from which the complete *ATPAC* clone was isolated. The isolation and characterization of *ATPAC* is described in Example 1.

A genomic clone of *ATPAC* (SEQ ID NO:10) has also been isolated from a bacterial artificial chromosome (BAC) library of the *Arabidopsis* genome (BAC clone IGF F3J22, obtained from the *Arabidopsis* stock center, Ohio State University). A 7 kb fragment containing part of *ATPAC* and additional 5' regulatory sequences was subcloned into a plasmid vector (pBluescript). A restriction map of *ATPAC* is found in Fig. 3. The corresponding cDNA clone of *ATPAC* is found in SEQ ID NO:1 and its restriction map is Fig. 4.

Among the unique features of this nucleic acid molecule as compared with other mdr-like genes from plants are its inducibility by certain compounds, including NPPB and herbicides, and its preferential expression in roots. The promoter regulatory region of *ATPAC* comprises residues 1-3429 of SEQ ID NO:10.

Although the *ATPAC* cDNA clone from *Arabidopsis thaliana* is described and exemplified herein, this invention is intended to encompass nucleic acid sequences and proteins from other plant species that are sufficiently similar to be used instead of *ATPAC* nucleic acid and proteins for the purposes described below. These include, but are not limited to, allelic variants and natural mutants of SEQ ID NO:1, which are likely to

be found in different species of plants or varieties of *Arabidopsis*.

Because such variants are expected to possess certain differences in nucleotide and amino acid sequence, this invention provides an isolated *p1PAC* nucleic acid molecule having at least about 60% (preferably 70% and more preferably over 80%) sequence homology in the coding regions with the nucleotide sequence set forth as SEQ ID NO:1 or SEQ ID NO:10 (and, most preferably, specifically comprising the coding region of SEQ ID NO:1). Also provided are nucleic acids that encode a polypeptide that is at least about 40% (preferably 50% and most preferably 60%) similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2. Also provided are nucleic acids that hybridize to the nucleic acids of SEQ ID NO:1, SEQ ID NO:10, or nucleic acids encoding the regions of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2, preferably under moderate stringency (more preferably, high stringency, and most preferably, very high stringency).

In other preferred embodiments, the nucleic acids have a restriction digest map that is identical for at least 3 enzymes (more preferably 6 enzymes and most preferably 9 enzymes) to the maps shown in Figs. 3 or 4. In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. 3 for enzymes *Xho*I, *Xcm*I and *Spe*I (preferably additionally *Sac*I, *Pac*I and *Bsa*I, and most preferably additionally *Acl*I, *Ban*I and *SnaB*I). In another preferred embodiment, the nucleic acids have a restriction digest map identical to those shown in Fig. 4 for enzymes *Xba*I, *Tat*I and *Nci*I (preferably additionally *Dra*I, *Bsm*I and *Bcl*I, and most preferably additionally *Acc*I, *Bsg*I and *Tli*I). The nucleic acids of the invention are at least 20 nucleic

acids in length (preferably at least 50 nucleic acids and most preferably at least 100 nucleic acids).

In accordance with the invention, novel plPAC genes from two plant species, *Brassica napus* and *Arabidopsis thaliana*, are presented. This constitutes the first description of this unique p-glycoprotein in plants. Indeed, the closest known protein sequence, also from *Arabidopsis*, is only 65% identical suggesting that the *ATPAC* gene is novel and is expected to have novel properties. The isolation of two *plPAC* genes from different species enables the isolation of further *plPAC* genes from other plant species. Isolated nucleic acids that are *plPAC* genes from any plant species are considered part of the instant invention. In particular, the nucleic acids of other *plPAC* genes can be isolated using sequences of *ATPAC* that distinguish *plPAC* genes from other plant *mdr* genes according to methods that are well known to those in the art of gene isolation. In particular, sequences that encode residues 1-76, 613-669 and 1144-1161 of SEQ ID NO:2 can be used. In a preferred embodiment, the *plPAC* gene is from any higher plant species (more preferred from a dicot species, and most preferred from a species in Brassicaceae (or Cruciferae)).

This invention also provides isolated polypeptide products of the open reading frames of SEQ ID NO:1 or SEQ ID NO:10, having at least about 70% (preferably 80% and most preferably 90%) sequence identity, or at least about 80% similarity (preferably 90% and more preferably 95%) with the amino acid sequence of SEQ ID NO:2. In another embodiment, the polypeptides of the invention are at least about 40% identical (preferably 50%, and most preferably 60%) to the regions of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

Because of the natural sequence variation likely to exist among *p1PAC* genes, one skilled in the art would expect to find up to about 30-40% nucleotide sequence variation, while still maintaining the unique properties of the *p1PAC* gene and encoded polypeptide of the present invention. Such an expectation is due in part to the degeneracy of the genetic code, as well as to the known evolutionary success of conservative amino acid sequence variations, which do not appreciably alter the nature of the encoded protein. Accordingly, such variants are considered substantially the same as one another and are included within the scope of the present invention.

Also provided are transgenic plants transformed with part or all of the nucleic acids of the invention. Transgenic plants that over-express a p1PAC coding sequence are one embodiment of this aspect of the invention. Example 3 provides for one prototype of such a plant. In a preferred embodiment, the *ATPAC* gene is used, and in a most preferred embodiment SEQ ID NO:1 or SEQ ID NO:10 is used. The *p1PAC* gene may be placed under a powerful constitutive promoter, such as the Cauliflower Mosaic Virus (CaMV) 35S promoter or the figwort mosaic virus 35S promoter. In a preferred embodiment, the 35SCaMV promoter is used. Transgenic plants expressing the *p1PAC* gene under an inducible promoter (either its own promoter or a heterologous promoter) are also contemplated to be within the scope of the present invention. Inducible plant promoters include the tetracycline repressor/operator controlled promoter. In a preferred embodiment, a native *p1PAC* promoter is used, and in a most preferred embodiment, residues 1-3429 of SEQ ID NO:10 is used. Plant species that are contemplated for overexpression of a *p1PAC* coding sequence include, but are not limited to, soybean.

In another embodiment, overexpression of *p1PAC* is induced to generate a co-suppression effect. This excess expression serves to promote down-regulation of both endogenous and exogenous *p1PAC* genes.

In some instances, it may be desirable to down-regulate or inhibit expression of endogenous *p1PAC* in plants possessing the gene. Accordingly, *p1PAC* nucleic acid molecules, or fragments thereof, may also be utilized to control the production of *p1PAC*-encoded P-glycoproteins. In one embodiment, full-length *p1PAC* antisense molecules or antisense oligonucleotides, targeted to specific regions of *p1PAC*-encoded RNA that are critical for translation, are used. The use of antisense molecules to decrease expression levels of a pre-determined gene is known in the art. In a preferred embodiment, antisense molecules are provided *in situ* by transforming plant cells with a DNA construct which, upon transcription, produces the antisense sequences. Such constructs can be designed to produce full-length or partial antisense sequences. One example of antisense p1PAC transgenic plants is given in Example 3.

In another embodiment, knock-out plants are obtained by screening a T-DNA mutagenized plant population for insertions in the *p1PAC* gene (see Krysan et al., 1996, PNAS 93:8145). One example of this embodiment of the invention is found in Example 3. Optionally, transgenic plants can be created containing mutations in the region encoding the active site of *p1PAC*. These last two embodiments are preferred over the use of anti-sense constructs due to the high homology among P-glycoproteins.

The promoter of *ATPAC* is also provided in accordance with the invention. This promoter has the useful properties of root expression and inducability by

NPPB. The prototypic example of this aspect of the invention is residues 1-3429 of SEQ ID NO:10. It is anticipated that plPAC genes from other plant species will likewise exhibit the aforementioned useful properties. As these promoter regions can easily be isolated from the plPAC genes that are provided with the invention, all plant *plPAC* gene promoters are provided with the invention. The nucleic acids of the invention therefore include a nucleic acid molecule that is at least about 70% identical (preferably 80% and most preferably 90%) to the residues 1-3429 of SEQ ID NO:10. Also provided are nucleic acids that hybridize to the nucleic acid residues 1-3429 of SEQ ID NO:10 preferably under moderate stringency (more preferably, high stringency, and most preferably, very high stringency).

The present invention also provides antibodies capable of immuno-specifically binding to polypeptides of the invention. Polyclonal or monoclonal antibodies directed toward any of the peptides encoded by *plPAC* may be prepared according to standard methods. Monoclonal antibodies may be prepared according to general methods of Köhler and Milstein, following standard protocols. In a preferred embodiment, antibodies are prepared, which react immuno-specifically with various epitopes of the *plPAC*-encoded polypeptides. In a preferred embodiment, the antibodies are immunologically specific to the polypeptide of residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

The following description sets forth the general procedures involved in practicing the present invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. Unless otherwise specified, general cloning procedures, such as those set

forth in Sambrook et al., Molecular Cloning, Cold Spring Harbor Laboratory (1989) (hereinafter "Sambrook et al.") or Ausubel et al. (eds) Current Protocols in Molecular Biology, John Wiley & Sons (1997) (hereinafter "Ausubel et al.") are used.

III. Preparation of *PlPAC* Nucleic Acid Molecules, encoded Polypeptides, Antibodies Specific for the Polypeptides and Transgenic Plants

1. Nucleic Acid Molecules

PlPAC nucleic acid molecules of the invention may be prepared by two general methods: (1) they may be synthesized from appropriate nucleotide triphosphates, or (2) they may be isolated from biological sources. Both methods utilize protocols well known in the art.

The availability of nucleotide sequence information, such as the cDNA having SEQ ID NO:1, enables preparation of an isolated nucleic acid molecule of the invention by oligonucleotide synthesis. Synthetic oligonucleotides may be prepared by the phosphoramadite method employed in the Applied Biosystems 38A DNA Synthesizer or similar devices. The resultant construct may be purified according to methods known in the art, such as high performance liquid chromatography (HPLC). Long, double-stranded polynucleotides, such as a DNA molecule of the present invention, must be synthesized in stages, due to the size limitations inherent in current oligonucleotide synthetic methods. Thus, for example, a long double-stranded molecule may be synthesized as several smaller segments of appropriate complementarity. Complementary segments thus produced may be annealed such that each segment possesses appropriate cohesive termini for attachment of an adjacent segment. Adjacent segments may be ligated by annealing cohesive termini in the

presence of DNA ligase to construct an entire long double-stranded molecule. A synthetic DNA molecule so constructed may then be cloned and amplified in an appropriate vector.

PlPAC genes also may be isolated from appropriate biological sources using methods known in the art. In fact, the *ATPAC* clone was isolated from an *Arabidopsis* cDNA library using a partial clone obtained from *Brassica napus*. In alternative embodiments, genomic clones of *plPAC* may be isolated.

In accordance with the present invention, nucleic acids having the appropriate level sequence homology with part or all the coding regions of SEQ ID NO:1 or SEQ ID NO:10 may be identified by using hybridization and washing conditions of appropriate stringency. For example, hybridizations may be performed, according to the method of Sambrook et al., using a hybridization solution comprising: 5X SSC, 5X Denhardt's reagent, 1.0% SDS, 100 µg/ml denatured, fragmented salmon sperm DNA, 0.05% sodium pyrophosphate and up to 50% formamide. Hybridization is carried out at 37-42°C for at least six hours. Following hybridization, filters are washed as follows: (1) 5 minutes at room temperature in 2X SSC and 1% SDS; (2) 15 minutes at room temperature in 2X SSC and 0.1% SDS; (3) 30 minutes-1 hour at 37°C in 2X SSC and 0.1% SDS; (4) 2 hours at 45-55°in 2X SSC and 0.1% SDS, changing the solution every 30 minutes.

One common formula for calculating the stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology (Sambrook et al., 1989):

$T_m = 81.5°C + 16.6\text{Log}\,[Na+] + 0.41(\%\ G+C) - 0.63\ (\%\ \text{formamide}) - 600/\#\text{bp in duplex}$

As an illustration of the above formula, using [N+] = [0.368] and 50% formamide, with GC content of 42% and an average probe size of 200 bases, the T_m is 57°C. The T_m of a DNA duplex decreases by 1 - 1.5°C with every 1% decrease in homology. Thus, targets with greater than about 75% sequence identity would be observed using a hybridization temperature of 42°C.

The stringency of the hybridization and wash depend primarily on the salt concentration and temperature of the solutions. In general, to maximize the rate of annealing of the probe with its target, the hybridization is usually carried out at salt and temperature conditions that are 20-25°C below the calculated T_m of the of the hybrid. Wash conditions should be as stringent as possible for the degree of identity of the probe for the target. In general, wash conditions are selected to be approximately 12-20°C below the T_m of the hybrid. In regards to the nucleic acids of the current invention, a moderate stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 2X SSC and 0.5% SDS at 55°C for 15 minutes. A high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 1X SSC and 0.5% SDS at 65°C for 15 minutes. A very high stringency hybridization is defined as hybridization in 6X SSC, 5X Denhardt's solution, 0.5% SDS and 100 µg/ml denatured salmon sperm DNA at 42°C, and wash in 0.1X SSC and 0.5% SDS at 65°C for 15 minutes.

Nucleic acids of the present invention may be maintained as DNA in any convenient cloning vector. In a preferred embodiment, clones are maintained in plasmid

cloning/expression vector, such as pGEM-T (Promega Biotech, Madison, WI) or pBluescript (Stratagene, La Jolla, CA), either of which is propagated in a suitable *E. coli* host cell.

P1PAC nucleic acid molecules of the invention include cDNA, genomic DNA, RNA, and fragments thereof which may be single- or double-stranded. Thus, this invention provides oligonucleotides (sense or antisense strands of DNA or RNA) having sequences capable of hybridizing with at least one sequence of a nucleic acid molecule of the present invention, such as selected segments of SEQ ID NO:1 or SEQ ID NO:10. Such oligonucleotides are useful as probes for detecting *p1PAC* genes or mRNA in test samples, e.g. by PCR amplification, mapping of genes or for the positive or negative regulation of expression of *p1PAC* genes at or before translation of the mRNA into proteins.

The *p1PAC* promoter is also expected to be useful in connection with the present invention, inasmuch as it is inducible in plants upon exposure to anion channel blockers. As mentioned above, seven-kilobase fragment of genomic DNA has been isolated, which contains part or all of the *p1PAC* promoter from *Arabidopsis thaliana*. This promoter can be used in chimeric gene constructs to facilitate inducible expression of any coding sequence of interest, upon exposure to NPPB or similar-acting compounds.

2. Proteins

Polypeptides encoded by *p1PAC* nucleic acids of the invention may be prepared in a variety of ways, according to known methods. If produced *in situ* the polypeptides may be purified from appropriate sources, e.g., plant roots or other plant parts.

Alternatively, the availability of nucleic acid molecules encoding the polypeptides enables production of the proteins using *in vitro* expression methods known in the art. For example, a cDNA or gene may be cloned into an appropriate *in vitro* transcription vector, such a pSP64 or pSP65 for *in vitro* transcription, followed by cell-free translation in a suitable cell-free translation system, such as wheat germ or rabbit reticulocytes. *In vitro* transcription and translation systems are commercially available, e.g., from Promega Biotech, Madison, Wisconsin or BRL, Rockville, Maryland.

According to a preferred embodiment, larger quantities of *plPAC*-encoded polypeptide may be produced by expression in a suitable procaryotic or eucaryotic system. For example, part or all of a DNA molecule, such as the cDNA having SEQ ID NO:1, may be inserted into a plasmid vector adapted for expression in a bacterial cell (such as *E. coli*) or a yeast cell (such as *Saccharomyces cerevisiae*), or into a baculovirus vector for expression in an insect cell. Such vectors comprise the regulatory elements necessary for expression of the DNA in the host cell, positioned in such a manner as to permit expression of the DNA in the host cell. Such regulatory elements required for expression include promoter sequences, transcription initiation sequences and, optionally, enhancer sequences.

The plPAC polypeptide produced by gene expression in a recombinant procaryotic or eucyarotic system may be purified according to methods known in the art. In a preferred embodiment, a commercially available expression/secretion system can be used, whereby the recombinant protein is expressed and thereafter secreted from the host cell, to be easily purified from the surrounding medium. If expression/secretion vectors are

not used, an alternative approach involves purifying the recombinant protein by affinity separation, such as by immunological interaction with antibodies that bind specifically to the recombinant protein. Such methods are commonly used by skilled practitioners.

The *p1PAC*-encoded polypeptides of the invention, prepared by the aforementioned methods, may be analyzed according to standard procedures.

C. Transgenic Plants

Transgenic plants expressing the *p1PAC* gene can be generated using standard plant transformation methods known to those skilled in the art. These include, but are not limited to, *Agrobacterium* vectors, PEG treatment of protoplasts, biolistic DNA delivery, UV laser microbeam, gemini virus vectors, calcium phosphate treatment of protoplasts, electroporation of isolated protoplasts, agitation of cell suspensions with microbeads coated with the transforming DNA, direct DNA uptake, liposome-mediated DNA uptake, and the like. Such methods have been published in the art. See, e.g., Methods for Plant Molecular Biology (Weissbach & Weissbach, eds., 1988); Methods in Plant Molecular Biology (Schuler & Zielinski, eds., 1989); Plant Molecular Biology Manual (Gelvin, Schilperoort, Verma, eds., 1993); and Methods in Plant Molecular Biology - A Laboratory Manual (Maliga, Klessig, Cashmore, Gruissem & Varner, eds., 1994).

The method of transformation depends upon the plant to be transformed. The biolistic DNA delivery method is useful for nuclear transformation. In another embodiment of the invention, *Agrobacterium* vectors are used to advantage for efficient transformation of plant nuclei.

In a preferred embodiment, the gene is introduced into plant nuclei in *Agrobacterium* binary vectors. Such vectors include, but are not limited to, BIN19 (Bevan, 1984, Nucleic Acid Res 12: 8711-8721) and derivatives thereof, the pBI vector series (Jefferson et al., 1987, PNAS 83:8447-51), and binary vectors pGA482 and pGA492 (An, 1986) and others (for review, see An, 1995, Methods Mol Biol 44:47-58). In preferred embodiments, the pPZP211 vector (Hajdukiewicz et al., 1994, PMB 25:989-994) or PCGN7366 (Calgene, CA) are used. DNA constructs for transforming a selected plant comprise a coding sequence of interest operably linked to appropriate 5' (e.g., promoters and translational regulatory sequences) and 3' regulatory sequences (e.g., terminators).

Using an *Agrobacterium* binary vector system for transformation, the *plPAC* coding region, under control of a constitutive or inducible promoter as described above, is linked to a nuclear drug resistance marker, such as kanamycin resistance. *Agrobacterium*-mediated transformation of plant nuclei is accomplished according to the following procedure:

(1) the gene is inserted into the selected *Agrobacterium* binary vector;

(2) transformation is accomplished by co-cultivation of plant tissue (e.g., leaf discs) with a suspension of recombinant *Agrobacterium*, followed by incubation (e.g., two days) on growth medium in the absence of the drug used as the selective medium (see, e.g., Horsch et al. 1985, Cold Spring Harb Symp Quant Biol. 50:433-7);

(3) plant tissue is then transferred onto the selective medium to identify transformed tissue; and

(4) identified transformants are regenerated

to intact plants.

It should be recognized that the amount of expression, as well as the tissue specificity of expression of the *p1PAC* gene in transformed plants can vary depending on the position of their insertion into the nuclear genome. Such position effects are well known in the art. For this reason, several nuclear transformants should be regenerated and tested for expression of the transgene.

IV. Uses of *P1PAC* Nucleic Acids, Encoded Proteins and Antibodies

1. *P1PAC* Nucleic Acids

P1PAC nucleic acids may be used for a variety of purposes in accordance with the present invention. The DNA, RNA, or fragments thereof may be used as probes to detect the presence of and/or expression of *p1PAC* genes. Methods in which *p1PAC* nucleic acids may be utilized as probes for such assays include, but are not limited to: (1) *in situ* hybridization; (2) Southern hybridization (3) northern hybridization; and (4) assorted amplification reactions such as polymerase chain reactions (PCR).

The *p1PAC* nucleic acids of the invention may also be utilized as probes to identify related genes from other plant species. As is well known in the art and described above, hybridization stringencies may be adjusted to allow hybridization of nucleic acid probes with complementary sequences of varying degrees of homology. Thus, *p1PAC* nucleic acids may be used to advantage to identify and characterize other genes of varying degrees of relation to the exemplary *ATPAC*, thereby enabling further characterization of this family

of genes in plants. Additionally, they may be used to identify genes encoding proteins that interact with the P-glycoprotein encoded by *p1PAC* (e.g., by the "interaction trap" technique).

2. PlPAC Proteins and Antibodies

Purified *p1PAC*-encoded P-glycoproteins, or fragments thereof, may be used to produce polyclonal or monoclonal antibodies which also may serve as sensitive detection reagents for the presence and accumulation of plant P-glycoproteins in cultured plant cells or tissues and in intact plants. Recombinant techniques enable expression of fusion proteins containing part or all of the *p1PAC*-encoded protein. The full length protein or fragments of the protein may be used to advantage to generate an array of monoclonal or polyclonal antibodies specific for various epitopes of the protein, thereby providing even greater sensitivity for detection of the protein in cells or tissue.

Polyclonal or monoclonal antibodies immunologically specific for *p1PAC*-encoded proteins may be used in a variety of assays designed to detect and quantitate the protein. Such assays include, but are not limited to: (1) flow cytometric analysis; (2) immunochemical localization in cultured cells or tissues; and (3) immunoblot analysis (e.g., dot blot, Western blot) of extracts from various cells and tissues.

Polyclonal or monoclonal antibodies that immunospecifically interact with one or more of the polypeptides encoded by *p1PAC* can be utilized for identifying and purifying such proteins. For example, antibodies may be utilized for affinity separation of proteins with which they immunospecifically interact. Antibodies may also be used to immunoprecipitate proteins

from a sample containing a mixture of proteins and other biological molecules.

3. p1PAC Transgenic Plants

Transgenic plants that over- or under- express p1PAC can be used in a varied of agronomic and research applications. From the foregoing discussion, it can be seen that *p1PAC* and its homologs, and transgenic plants containing them will be useful for improving stress resistance or tolerance in plants. This provides an avenue for developing marginal or toxic soil environments for crop production. Both over- and under-expressing p1PAC transgenic plants have great utility in the research of herbicides and other xenobiotic compounds.

As discussed above and in greater detail in Example 1, the similarity between plant and mammalian *mdr* genes indicates that their functional aspects will also be conserved. Thus, *p1PAC* is expected to play an important role in the exclusion of toxic metabolic or xenobiotic compounds from cells. The fact that *p1PAC* also is inducible and appears to be preferentially expressed in roots, where contact with such compounds often occurs, makes *p1PAC* particularly desirable for genetic engineering of plants to increase their tolerance to such compounds. Accordingly, plants engineered to overexpress the *p1PAC* gene should be resistant to a wide range of chemicals, both intentionally applied as herbicides or unintentionally as wastes. Examples of the kinds of xenobiotics that should be detoxified by the *p1PAC* of the invention include, but are not limited to, hydrophobic (i.e., lipophilic) herbicides and other compounds, such as 3(3,4-dichlorophenyl)-1,1, dimethyl urea (also known as DCMU or Diuron, available from Sigma Chemical Co., St. Louis, MO) or other hydrophobic

compounds that disrupt photosynthetic electron transport, as well as Metachlor (Ciba Geigy, Basel Switzerland), Taurocholate (Sigma Chemical Co.), Primisulfuron (Ciba Geigy), and IRL-1803.

As illustrated in Example 2, plant cells that over-express a *p1PAC* gene have surprisingly higher growth rate with or without the xenobiotic compound Rhodamine 6G. It is contemplated that *p1PAC* overexpression may be a generally useful way to increase plant and plant cell culture growth, even without the presence of xenobiotic compounds.

The following specific examples are provided to illustrate embodiments of the invention. They are not intended to limit the scope of the invention in any way.

EXAMPLE 1
Cloning and Analysis of a *P1PAC From Arabidopsis thaliana*

The *p1PAC* of the present invention was identified by its up-regulation in response to a chloride ion channel blocker. *Brassica napus* plants were grown either in the presence or absence of 20 µM 5-nitro-2-(3-phenylpropylamino) benzoic acid (NPPB). After five days, the roots of the seedlings were harvested and total RNA was extracted separately from the treated and untreated plants. From the total RNA preparations, poly (A)+ RNA was isolated and used as the starting material to create a cDNA subtraction library, using the CLONTECH PCR-SELECT™ cDNA Subtraction Kit and accompanying instructions (CLONTECH Laboratories, Inc., Palo Alto, CA).

Using the subtractive hybridization kit, a gene fragment was identified that was up-regulated in response to treatment of the plants with NPPB. This fragment (0.5 kb) was used to screen a cDNA library of *Arabidopsis thaliana*, from which a full-length cDNA clone was isolated. The nucleotide sequence of this cDNA clone, referred to as *ATPAC* (*Arabidopsis thaliana* putative anion channel) is set forth below as SEQ ID NO:1.

The 3.76 kb cDNA clone encodes a polypeptide 1,254 amino acids in length. The deduced amino acid sequence encoded by SEQ ID NO:1 is shown in Figure 1 as "atpac" (SEQ ID NO:2), in a lineup with the following sequences: (1) hmdr1 (SEQ ID NO:3); (2) mmdr1 (SEQ ID NO:4); (3) hmdr3 (SEQ ID NO:5); (4) mmdr2 (SEQ ID NO:6); (5) atpgp1 (SEQ ID NO:7); and (6) atpgp2 (SEQ ID NO:8). A consensus sequence (SEQ ID NO:9) is also shown.

A search of various sequence databases indicates that *ATPAC* is a new and distinct member of the *mdr* family of ABC transporters. In none of the databases, including the EST collection, does an exact match exist. The ABC transporter family is very large, consisting of at least two sub-groups, *mrp* and homologs and *mdr* and homologs. The only examples of plant *mdr*-like genes are *atpgp1* and *atpgp2* from *A. thaliana* and two homologs from potato and barley, respectively. Though the *atpgp1* and *atpgp2* genes are similar to *ATPAC*, they are only 51 and 50% identical, respectively, indicating that *ATPAC* is a distinct gene by comparison. Sequence homology with the potato and barley *mdr*-like genes is even more divergent. Another difference between the *agpgp1* gene and the *ATPAC* gene is their respective preferential expression in inflorescens and roots, respectively.

EXAMPLE 2
Effect of *ATPAC* Expression in Bacterial Cells on Their Ability to Detoxify Rhodamine 6G

The compound Rhodamine 6G is a well known substrate of mammalian p-glycoproteins (Kolaczkowski et al., J. Biol. Chem. 271: 31543-31548, 1996). The ability of a cell to detoxify the compound is indicative of activity of p-glycoproteins. A bacterial cell line was transformed with an expression vector comprising *ATPAC*. The growth rate of transformed and non-transformed cells was then measured, in the presence or absence of Rhodamine 6G. Results are shown in Figure 2. As can be seen, *ATPAC*-expressing cells grown in the absence of the drug had the best growth rate. Moreover, even in the presence of the drug, the cells grew more quickly than non-transformed cells in the presence or absence of Rhodamine 6G. These results demonstrate that *ATPAC* encodes a functional and robust p-glycoprotein.

Example 3
Transgenic Plants the Overexpress and Underexpress ATPAC

Transformation construct. The *Agrobacterium* binary vector pPZP211 (Hajdukiewicz et al., 1994 Plant Mol. Biol. 25:989-994) was digested with *EcoR*I and *Sma*I, and self-ligated. This molecule was named pPZP211'. The *Agrobacterium* binary vector pCGN7366 (Calgene, CA) was digested with *Xho*I and cloned in SalI-digested pPZP211'. We named this binary vector pPZP-PCGN. The 3.8 kb full-length *ATPAC* cDNA was cloned into the pGH19 vector. After digestion with *Sma*I (in the multiple cloning site upstream) and *EcoR*I, a 3.1 kb cDNA fragment was cut out.

This *Sma*I-*Eco*RI 3.1 kb fragment was cloned into the SmaI/EcoRI site of pPZP-pCGN. The rest of *ATPAC* gene was amplified using polymerase chain reaction to have translationally fused HA-tag at its 3'-terminal. After ligating *Eco*R1 linkers to the ends of the resulting PCR product, the 0.7 kb fragment was cloned into the *Eco*RI site of the *Sma*I-*Eco*RI 3.1 kb *ATPAC* fragment in pPZP-pCGN. The final construct was named pATPAC-OE.

Plant transformation. pATPAC-OE was introduced into *Agrobacterium tumefaciens* strain by a direct transformation method. *Agrobacterium*-mediated transformation was performed using vacuum infiltration (Bechtold et al., 1993,. CR Acad. Sci. [III] 316: 1194-1199.)

T1 plants which survived on kanamycin-containing plates were selected, transplanted into soil and grown to set T2 seed. T3 seeds were collected from kanamycin-resistant T2 plants. T3 plants which showed 100% kanamycin-resistance were selected and were considered homozygous for the transgene.

Antisense Plants. The full length cDNA in pBluescript SK(-) vector (Stratagene, CA) is digested with *Eco*RI (there is a cleavage site in the upstream polylinker) and *Ssp*I. The resulting 1.3 Kb fragment representing a 5' portion of the *AtPAC* cDNA was cloned into the aforementioned pPZP-PCGN, which had been digested with *Eco*RI/*Sma*I, ensuring that this fragment of the cDNA was inserted in the antisense orientation. This construct was named pATPAC-AE. pATPAC-AE was introduced into *Arabidopsis* plants by *Agrobacterium* transformation, as described above.

Knock-out Plants. The method of Krysan et al (1996, PNAS 93:8145, incorporated by reference herein) was followed using the following primers:

Gene-specific primers:

AtpacF: CACTGCTCAATGATCTCGTTTTCTCACTA (SEQ ID NO:11)

AtpacR: CTTGAATCACACCAATGCAATCAACACCTC (SEQ ID NO:12)

Primers for T-DNA left boarder:

JL202: CATTTTATAATAACGCTGCGGACATCTAC (SEQ ID NO:13)

JL270: TTTCTCCATATTGACCATCATACTCATTG (SEQ ID NO:14)

While certain of the preferred embodiments of the present invention have been described and specifically exemplified above, it is not intended that the invention be limited to such embodiments. Various modifications may be made thereto without departing from the scope and spirit of the present invention, as set forth in the following claims.

What is claimed:

1. A nucleic acid isolated from a plant, which encodes a p-glycoprotein that is inducible by exposure of the plant to NPPB.

2. The isolated nucleic acid of claim 1, which is preferentially expressed in plant roots upon exposure of the plant to NPPB.

3. The isolated nucleic acid of claim 1, wherein the plant is selected from the group consisting of *Brassica napus* and *Arabidopsis thaliana* and is 3850-4150 nucleotides long.

4. The isolated nucleic acid of claim 1, which has the restriction sites shown in Figure 4 for at least three enzymes.

5. The isolated nucleic acid of claim 4, which encodes a polypeptide having SEQ ID NO:2.

6. The isolated nucleic acid of claim 5, which is a cDNA comprising a coding region selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:10.

7. An isolated protein, which is a product of expression of part or all of the isolated nucleic acid molecule of claim 1.

8. Antibodies immunologically specific for the protein of claim 7.

9. A expression cassette, which comprises a

plPAC gene coding sequence operably linked to a promoter.

10. The expression cassette of claim 9, which comprises a *plPAC* gene from *Arabidopsis thaliana*.

11. The expression cassette of claim 10, in which the promoter is the cauliflower mosaic virus 35S promoter.

12. The expression cassette of claim 10, in which the *plPAC* gene is part or all of SEQ ID NO:1 or SEQ ID NO:10.

13. A vector comprising the expression cassette of claim 9.

14. The vector of claim 13, which is comprised of an *Agrobacterium* binary vector selected from the group consisting of pPZP211 and pCGN7366.

15. A method for producing a plant with enhanced resistance to xenobiotic compounds by transforming *in vitro* the plant with the expression cassette of claim 9.

16. The method of claim 15, wherein the transformation step further uses the vector of claim 13.

17. A transgenic plant produced by the method of claim 15.

18. A reproductive unit form the transgenic plant of claim 17.

19. A cell from the transgenic plant of claim 17.

20. A recombinant DNA molecule comprising the nucleic acid molecule of claim 1, operably linked to a vector for transforming cells.

21. A cell transformed with the recombinant DNA molecule of claim 20.

22. The cell of claim 21, selected from the group consisting of bacterial cells, yeast cells and plant cells.

23. A transgenic plant regenerated from the transformed cell of claim 22.

24. An isolated nucleic acid molecule of at least 20 nucleotides in length having a sequence selected from the group consisting of:

a) SEQ ID NO:1 and SEQ ID NO:10;

b) a nucleic acid sequence that is at least about 60% homologous to the coding regions of SEQ ID NO:1 or SEQ ID NO:10;

c) a sequence hybridizing with SEQ ID NO:1 or SEQ ID NO:10 at moderate stringency;

d) a sequence encoding part or all of a polypeptide having SEQ ID NO:2;

e) a sequence encoding an amino acid sequence that is at least about 70% identical to SEQ ID NO:2;

f) a sequence encoding an amino acid sequence that is at least about 80% similar to SEQ ID NO:2;

g) a sequence encoding an amino acid sequence that is at least about 40% similar to residues 1-76, 613-

669 or 1144-1161 of SEQ ID NO:2; and

h) a sequence hybridizing at moderate stringency to a sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

25. A polypeptide produced by expression of the nucleic acid sequence of claim 24.

26. Antibodies immunologically specific for the polypeptide of claim 24.

27. An oligonucleotide between about 10 and about 100 nucleotides in length, which specifically hybridizes at moderate stringency with a portion of the nucleic acid molecule of claim 24.

28. A recombinant DNA molecule comprising the nucleic acid molecule of claim 24, operably linked to a vector for transforming cells.

29. A cell transformed with the recombinant DNA molecule of claim 28.

30. The cell of claim 29, selected from the group consisting of bacterial cells, yeast cells and plant cells.

31. A transgenic plant regenerated from the cell of claim 30.

32. An isolated plant p-glycoprotein, which is inducible upon exposure of the plant to NPPB.

33. The p-glycoprotein of claim 32, which

confers upon a cell in which it is found resistance to Rhodamine 6G.

34. The p-glycoprotein of claim 33, which is preferentially produced in roots upon the exposure to the NPPB.

35. The p-glycoprotein of claim 34, from a plant selected from the group consisting of *Brassica napus* and *Arabidopsis thaliana*.

36. The p-glycoprotein of claim 35, having an amino acid sequence that selected from the group consisting of:

a) an amino acid sequence that is at least 80% similar to SEQ ID NO:2;

b) an amino acid sequence that is at least 70% identical to SEQ ID NO:2;

c) an amino acid sequence that is at least 40% similar to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2; and

d) an amino acid sequence encoded by a nucleic acid sequence hybridizing at moderate stringency to a amino acid sequence encoding residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

37. Antibodies immunologically specific for the p-glycoprotein of claim 32.

38 The antibodies of claim 35, that are immunologically specific to residues 1-76, 613-669 or 1144-1161 of SEQ ID NO:2.

39. A plant p-glycoprotein gene promoter which

is inducible by NPPB.

40. The plant p-glycoprotein gene promoter of claim 39, that is part or all of residues 1-3429 of SEQ ID NO:10.

41. A plant with reduced levels of plPAC protein.

42. The plant of claim 41, wherein the native *plPAC* gene is mutated.

43. The plant of claim 42, wherein the *plPAC* gene is mutated due to the insertion of a T-DNA.

44. A method for making the plant of claim 42, wherein a population of mutated plants are screened using at least one of SEQ ID NOS:11-14 as PCR primers.

45. The method of claim 44, wherein the population of plants is mutated by T-DNA insertion.

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hmdr1          1 MDLEGDRNGGAKKKNF....FKLNNKSEKDKKEKKPT..VSVFSMFRYSNWLDKLYMVVGTLAAIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDINDTGFF
atpac          1 ~~~~~~~~~~~~~~~~MSETNTTDAKTVPAEAEKKKEQSLPFFKLFSFADKFDYLLMFVGSLGAIVHGSSMPVFFLLFGQMVNGFGKNQMDL.................
consensus      1 md e    g a          l   s  dr kkk    vgv  lFryadw Dkl M lGtlaAiiHGs lPlmmivFgemtd fa                    s

hmdr1        105 MN..LEEDMTRYAYYYSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQFFHAIMRQEIGWFDVH.DVGELNTRLTDDVSKINEVIGDKIGMFFQSMATFFTGFIVGFTRG
mmdr1        102 SNSSLEEEMAIYAYYYTGIGAGVLIVAYIQVSLWCLAAGRQIHKIRQKFFHAIMNQEIGWFDVH.DVGELNTRLTDDVSKINDGIGDKIGMFFQSITTFLAGFIIGFISG
atpac         77 ..HQMVHEVSRYSLYFVYLGLVVCFSSYAEIACWMYSGERQVAALRKKYLEAVLKQDVGFFDTDARTGDIVFSVSTDTLLVQDAISEKVGNFIHYLSTFLAGLVVGFVSA
atpgp1        80 ..EKMMEEVLKYALYFLVVGAAIWASSWAEISCWMWSGERQTTKMRIKYLEAALNQDIQFFDTEVRTSDVVFAINTDAVMVQDAISEKLGNFIHYMATFVSGFIVGFTAV
atpgp2        73 ..KQASHRVAKYSLDFVYLSVAILFSSWLEVACWMHTGERQAAKMRRAYLRSMLSQDISLFDTEASTGEVISAITSDILVVQDALSEKVGNFLHYISRFIAGFAIGFTSV
consensus    111   k leeemtrYayyysglgagvlv ayiqvs W laagRQirkiR kffhailrQeigwFDi   tgelntrltdDiskindgigdKvGmFfq vatFlaGfivGFi g

hmdr3        214 WKLTLVIMAISPILGLSAAVWAKILSAFSDKELAAYAKAGAVAEEALGAIRTVIAFGGQNKELERYQKHLENAKEIGIKKAISANISMGIAFLLIYASYALAFWYGSTLV
mmdr2        211 WKLTLVIMAISPILGLSTAVWAKILSTFSDKELAAYAKAGAVAEEAPGAIRTVIAFGGQNKELERYQKHLENAKKIGIKKAISANISMGIAFLLIYASYALAFWYGSTLV
hmdr1        212 WKLTLVILAISPVLGLSAAVWAKILSSFTDKELLAYAKAGAVAEEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIGAAFLLIYASYALAFWYGTTLV
mmdr1        211 WKLTLVILAVSPLIGLSSALWAKVLTSFTNKELQAYAKAGAVAEEVLAAIRTVIAFGGQQKELERYNKNLEEAKNVGIKKAITASISIGIAYLLVYASYALAFWYGTSLV
atpac        185 WKLALLSVAVIPGIAFAGGLYAYTLTGITSKSRESYANAGVIAEQAIAQVRTVYSYVGESKALNAYSDAIQYTLKLGYKAGMAKGLGLGCTYGIACMSWALVFWYAGVFI
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consensus    221 WkltLvilaisPiiglsaavwakils fs kel ayakAGavaEe lgaiRtViafgGq kelerYqk le akkiGiKkaisa ismG aflliyasyALafWygstlv

                                                                                                                        W_A
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consensus    331 is eytiG amtvffsiligafsvGqaap idAFanargAay ifkiIdn psidsfs  Ghkpd ikGnlefkdvhFsYPSR evkIlkglnlkv sGqtvAlVG SGc
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Figure 1 (sheet 1 of 4)

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mmdr2      431 GKSTTVQLLQRLYDPTEGKISIDGQDIRNFNVRCLREIIGVVSQEPVLFSTTIAENIRYGRGNVTMDEIEKAVKEANAYDFIMKLPQKFDTLVGDRGAQLSGGQKQRIAI
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atpac      405 GKSTVVSLIERFYDPNSGQILLDGVEIKTLQLKFLREQIGLVNQEPALFATTILENILYGKPDATMVEVEAAASAANAHSFITLLPKGYDTQVGERGVQLSGGQKQRIAI
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consensus  441 GKSTtvqLiqRlYdP eG v iDGqdirtinvryLReiIGvVsQEPvLFaTtIaENI yGr dvtmdEiekAvkeanAyeFImkLP  fdTlVGeRGaQLSGGQKQRIAI

                                                                  W_B
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mmdr2      541 ARALVRNPKILLLDEATSALDTESEAEVQAALDKAREGRTTIVIAHRLSTIRNADVIAGFEDGVIVEQGSHSELMKK..EGIYFRLVNMQTAGSQILSEE.........FE
hmdr1      542 ARALVRNPKILLLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAGFDDGVIVEKGNHDELMKE..KGIYFKLVTMQTAGNEVELEN.........AA
mmdr1      541 ARALVRNPKILLLDEATSALDTESEAVVQAALDKAREGRTTIVIAHRLSTVRNADVIAGFDGGVIVEQGNHDELMRE..KGIYFKLVMTQTRGNEIEPGN.........NA
atpac      515 ARAMLKDPKILLLDEATSALDASSESIVQEALDRVMVGRTTVVVAHRLCTIRNVDSIAVIQQGQVVETGTHEELIAK..SGAYASLIRFQEMVGTRDFSNPSTRRTRSTR
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atpgp2     620 IKYS.....................RELSRTRSSFCSER.ESVTRPDGADPSKKVKVTVG...RLYSMIRPDWMYGVCGTICAFIAGSQMPLFALGVSQAL.VSYYSGWDETQ
consensus  661    s e  a  m     ks l R  s   s       qd   r d   d le  vp vsfwrvlkln teWpY vvGtvcaiinG lqp FaiilS iiavf   dd  vk

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atpac      725 RK.TKEYVFIYIGAGLYAVGAYLIQHYFFSIMGENLTTRVRRMMLSAILRNEVGWFDEDEHNSSLIAARLATDAADVKSAIAERISVILQNMTSLLTSFIVAFIVEWRVS
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Figure 1 (sheet 2 of 4)

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atpac       834 LLILGTFPLLVLANFAQQLSLKGFAGDTAKAHAKTSMIAGEGVSNIRTVAAFNAQSKILSLFCHELRVPQKRSLSLYRSQTSGFLFGLSQLALYGSEALILWYGAHLVSK
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Figure 1 (sheet 3 of 4)

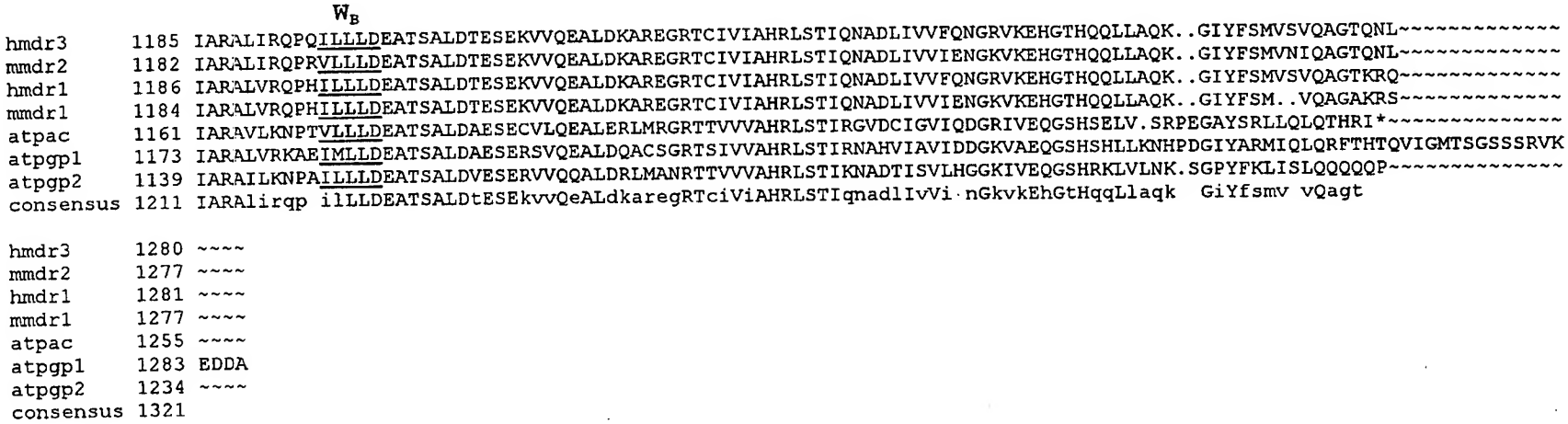
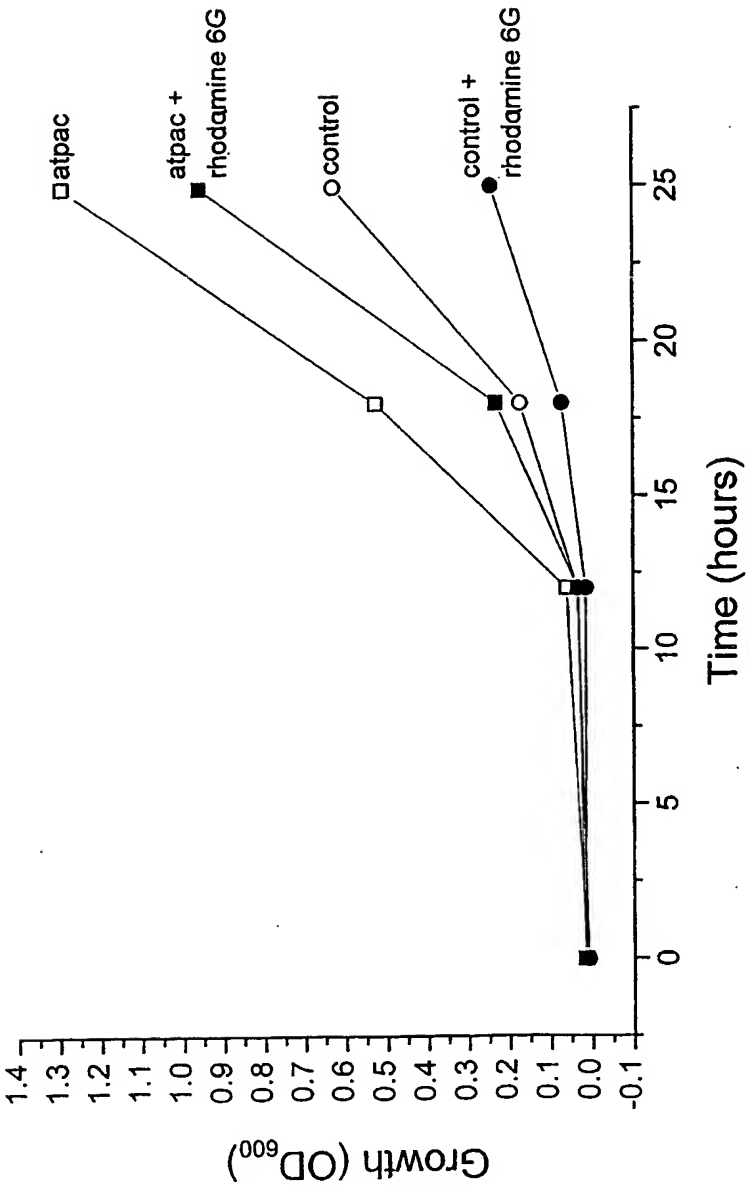


Figure 1 (sheet 4 of 4)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control + rhodamine 6G
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Figure 2

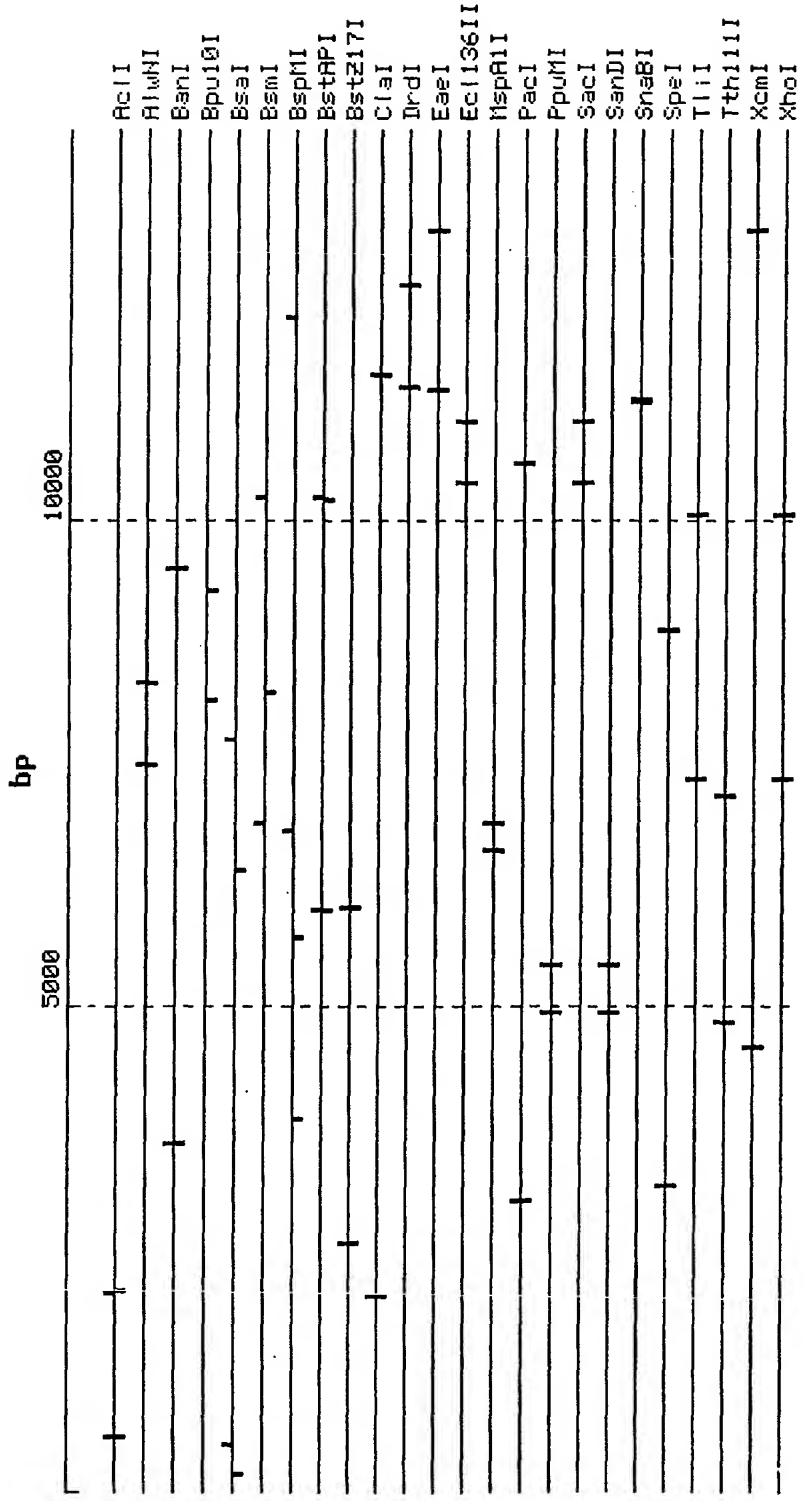
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Figure 3

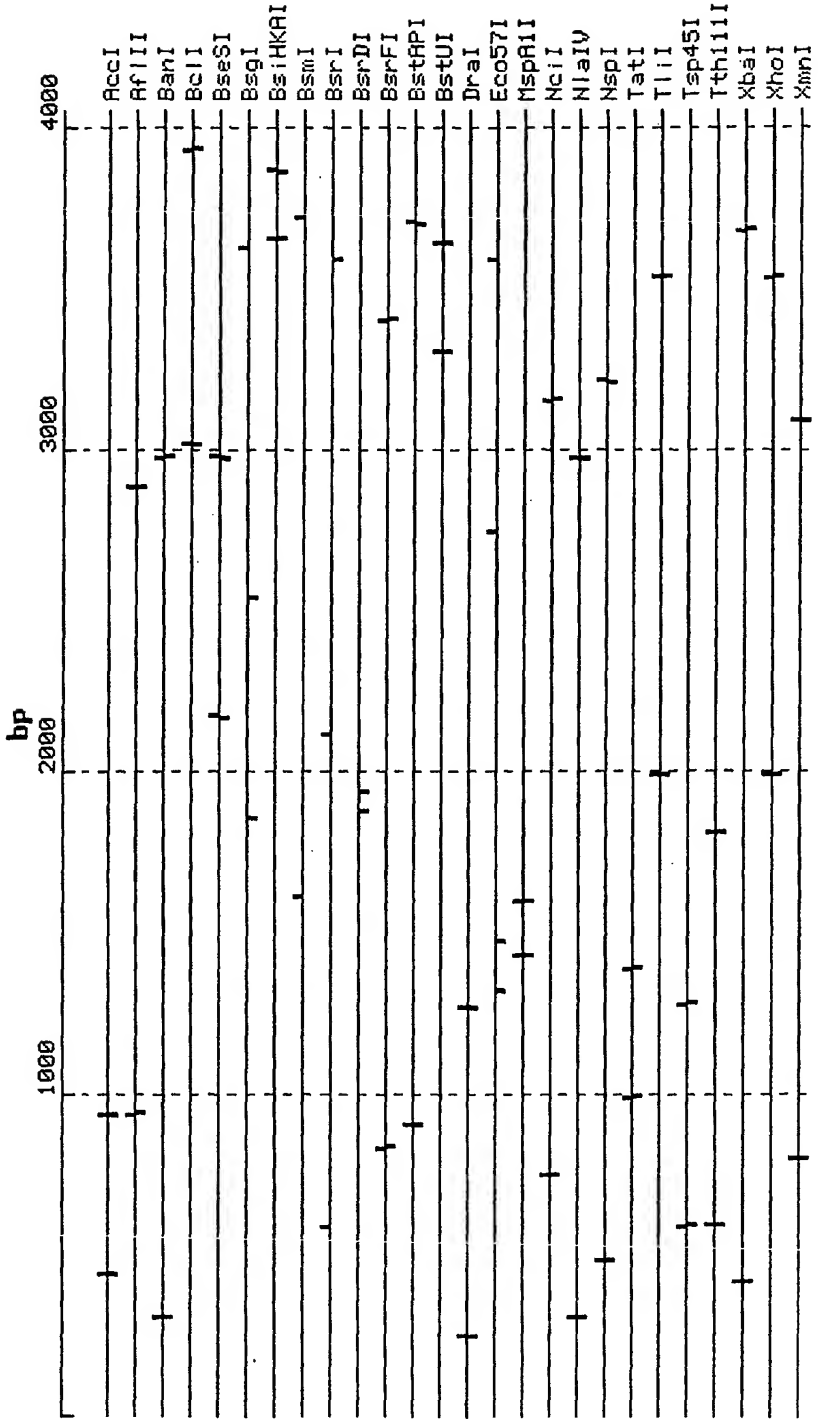
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Figure 4

SEQUENCE LISTING

<110> Wisconsin Alumni Research Foundation
Spalding, Edgar P.
Noh, Bosl

<120> Xenobiotic Detoxification Gene from Plants

<130> WARF S212

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<151> 1998-09-25

<160> 14

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gcaaatgctc acggtttcat cagtggttta cctgaaggtt acaaaactcc agtaggcgaa    3600
agaggagtgc agttatcagg tggacagaaa cagaggatcg cgatagcaag agctgtgctc    3660
aagaacccta cagtgttgct tctagacgaa gcaactagcg cactagatgc agaatcagaa    3720
tgcgtgctgc aagaggcgtt agagaggctc atgagaggtc ggaccaccgt ggtagttgct    3780
caccgcttgt ccaccataag aggtgttgat tgcattggtg tgattcaaga cgggcggatt    3840
gtggagcaag gcagccattc agagctcgtt agccgaccag agggagctta ttcaaggctg    3900
ttacagcttc aaacacatag gatttgaagc ttgatcatgg attaaaaaca aaaaatcggt    3960
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aatatgaata ggtgtagata atgaagcttt t                                   4051
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Glu Lys Lys Lys Glu Gln Ser Leu Pro Phe Phe Lys Leu Phe Ser Phe
            20                  25                  30
Ala Asp Lys Phe Asp Tyr Leu Leu Met Phe Val Gly Ser Leu Gly Ala
        35                  40                  45
Ile Val His Gly Ser Ser Met Pro Val Phe Phe Leu Leu Phe Gly Gln
    50                  55                  60
Met Val Asn Gly Phe Gly Lys Asn Gln Met Asp Leu His Gln Met Val
65                  70                  75                  80
His Glu Val Ser Arg Tyr Ser Leu Tyr Phe Val Tyr Leu Gly Leu Val
                85                  90                  95
Val Cys Phe Ser Ser Tyr Ala Glu Ile Ala Cys Trp Met Tyr Ser Gly
            100                 105                 110
Glu Arg Gln Val Ala Ala Leu Arg Lys Lys Tyr Leu Glu Ala Val Leu
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        115                 120                 125
Lys Gln Asp Val Gly Phe Phe Asp Thr Asp Ala Arg Thr Gly Asp Ile
    130                 135                 140
Val Phe Ser Val Ser Thr Asp Thr Leu Leu Val Gln Asp Ala Ile Ser
145                 150                 155                 160
Glu Lys Val Gly Asn Phe Ile His Tyr Leu Ser Thr Phe Leu Ala Gly
                165                 170                 175
Leu Val Val Gly Phe Val Ser Ala Trp Lys Leu Ala Leu Leu Ser Val
            180                 185                 190
Ala Val Ile Pro Gly Ile Ala Phe Ala Gly Gly Leu Tyr Ala Tyr Thr
        195                 200                 205
Leu Thr Gly Ile Thr Ser Lys Ser Arg Glu Ser Tyr Ala Asn Ala Gly
    210                 215                 220
Val Ile Ala Glu Gln Ala Ile Ala Gln Val Arg Thr Val Tyr Ser Tyr
225                 230                 235                 240
Val Gly Glu Ser Lys Ala Leu Asn Ala Tyr Ser Asp Ala Ile Gln Tyr
                245                 250                 255
Thr Leu Lys Leu Gly Tyr Lys Ala Gly Met Ala Lys Gly Leu Gly Leu
            260                 265                 270
Gly Cys Thr Tyr Gly Ile Ala Cys Met Ser Trp Ala Leu Val Phe Trp
        275                 280                 285
Tyr Ala Gly Val Phe Ile Arg Asn Gly Gln Thr Asp Gly Gly Lys Ala
    290                 295                 300
Phe Thr Ala Ile Phe Ser Ala Ile Val Gly Gly Met Ser Leu Gly Gln
305                 310                 315                 320
Ser Phe Ser Asn Leu Gly Ala Phe Ser Lys Gly Lys Ala Ala Gly Tyr
                325                 330                 335
Lys Leu Met Glu Ile Ile Asn Gln Arg Pro Thr Ile Ile Gln Asp Pro
            340                 345                 350
Leu Asp Gly Lys Cys Leu Asp Gln Val His Gly Asn Ile Glu Phe Lys
        355                 360                 365
Asp Val Thr Phe Ser Tyr Pro Ser Arg Pro Asp Val Met Ile Phe Arg
    370                 375                 380
Asn Phe Asn Ile Phe Phe Pro Ser Gly Lys Thr Val Ala Val Val Gly
385                 390                 395                 400
Gly Ser Gly Ser Gly Lys Ser Thr Val Val Ser Leu Ile Glu Arg Phe
                405                 410                 415
Tyr Asp Pro Asn Ser Gly Gln Ile Leu Leu Asp Gly Val Glu Ile Lys
            420                 425                 430
Thr Leu Gln Leu Lys Phe Leu Arg Glu Gln Ile Gly Leu Val Asn Gln
        435                 440                 445
Glu Pro Ala Leu Phe Ala Thr Thr Ile Leu Glu Asn Ile Leu Tyr Gly
    450                 455                 460
Lys Pro Asp Ala Thr Met Val Glu Val Glu Ala Ala Ala Ser Ala Ala
465                 470                 475                 480
Asn Ala His Ser Phe Ile Thr Leu Leu Pro Lys Gly Tyr Asp Thr Gln
                485                 490                 495
Val Gly Glu Arg Gly Val Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile
            500                 505                 510
Ala Ile Ala Arg Ala Met Leu Lys Asp Pro Lys Ile Leu Leu Leu Asp
        515                 520                 525
Glu Ala Thr Ser Ala Leu Asp Ala Ser Ser Glu Ser Ile Val Gln Glu
    530                 535                 540
Ala Leu Asp Arg Val Met Val Gly Arg Thr Thr Val Val Val Ala His
545                 550                 555                 560
Arg Leu Cys Thr Ile Arg Asn Val Asp Ser Ile Ala Val Ile Gln Gln
                565                 570                 575
Gly Gln Val Val Glu Thr Gly Thr His Glu Glu Leu Ile Ala Lys Ser
            580                 585                 590
Gly Ala Tyr Ala Ser Leu Ile Arg Phe Gln Glu Met Val Gly Thr Arg
        595                 600                 605
Asp Phe Ser Asn Pro Ser Thr Arg Arg Thr Arg Ser Thr Arg Leu Ser
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610 615 620
His Ser Leu Ser Thr Lys Ser Leu Ser Leu Arg Ser Gly Ser Leu Arg
625 630 635 640
Asn Leu Ser Tyr Ser Tyr Ser Thr Gly Ala Asp Gly Arg Ile Glu Met
645 650 655
Ile Ser Asn Ala Glu Thr Asp Arg Lys Thr Arg Ala Pro Glu Asn Tyr
660 665 670
Phe Tyr Arg Leu Leu Lys Leu Asn Ser Pro Glu Trp Pro Tyr Ser Ile
675 680 685
Met Gly Ala Val Gly Ser Ile Leu Ser Gly Phe Ile Gly Pro Thr Phe
690 695 700
Ala Ile Val Met Ser Asn Met Ile Glu Val Phe Tyr Tyr Thr Asp Tyr
705 710 715 720
Asp Ser Met Glu Arg Lys Thr Lys Glu Tyr Val Phe Ile Tyr Ile Gly
725 730 735
Ala Gly Leu Tyr Ala Val Gly Ala Tyr Leu Ile Gln His Tyr Phe Phe
740 745 750
Ser Ile Met Gly Glu Asn Leu Thr Thr Arg Val Arg Arg Met Met Leu
755 760 765
Ser Ala Ile Leu Arg Asn Glu Val Gly Trp Phe Asp Glu Asp Glu His
770 775 780
Asn Ser Ser Leu Ile Ala Ala Arg Leu Ala Thr Asp Ala Ala Asp Val
785 790 795 800
Lys Ser Ala Ile Ala Glu Arg Ile Ser Val Ile Leu Gln Asn Met Thr
805 810 815
Ser Leu Leu Thr Ser Phe Ile Val Ala Phe Ile Val Glu Trp Arg Val
820 825 830
Ser Leu Leu Ile Leu Gly Thr Phe Pro Leu Leu Val Leu Ala Asn Phe
835 840 845
Ala Gln Gln Leu Ser Leu Lys Gly Phe Ala Gly Asp Thr Ala Lys Ala
850 855 860
His Ala Lys Thr Ser Met Ile Ala Gly Glu Gly Val Ser Asn Ile Arg
865 870 875 880
Thr Val Ala Ala Phe Asn Ala Gln Ser Lys Ile Leu Ser Leu Phe Cys
885 890 895
His Glu Leu Arg Val Pro Gln Lys Arg Ser Leu Ser Leu Tyr Arg Ser
900 905 910
Gln Thr Ser Gly Phe Leu Phe Gly Leu Ser Gln Leu Ala Leu Tyr Gly
915 920 925
Ser Glu Ala Leu Ile Leu Trp Tyr Gly Ala His Leu Val Ser Lys Gly
930 935 940
Val Ser Thr Phe Ser Lys Val Ile Lys Val Phe Val Val Leu Val Ile
945 950 955 960
Thr Ala Asn Ser Val Ala Glu Thr Val Ser Leu Ala Pro Glu Ile Ile
965 970 975
Arg Gly Gly Glu Ala Val Gly Ser Val Phe Ser Val Leu Asp Arg Gln
980 985 990
Thr Arg Ile Asp Pro Asp Asp Ala Asp Ala Asp Pro Val Glu Thr Ile
995 1000 1005
Arg Gly Asp Ile Glu Phe Arg His Val Asp Phe Ala Tyr Pro Ser Arg
1010 1015 1020
Pro Asp Val Met Val Phe Arg Asp Phe Asn Leu Arg Ile Arg Ala Gly
1025 1030 1035 1040
His Ser Gln Ala Leu Val Gly Ala Ser Gly Ser Gly Lys Ser Ser Val
1045 1050 1055
Ile Ala Met Ile Glu Arg Phe Tyr Asp Leu Leu Ala Gly Lys Val Met
1060 1065 1070
Ile Asp Gly Lys Asp Ile Arg Arg Leu Asn Leu Lys Ser Leu Arg Leu
1075 1080 1085
Lys Ile Gly Leu Val Gln Gln Glu Pro Ala Leu Phe Ala Ala Thr Ile
1090 1095 1100
Phe Asp Asn Ile Ala Tyr Gly Lys Asp Gly Ala Thr Glu Ser Glu Val

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1105                1110                1115                1120
Ile Asp Ala Ala Arg Ala Ala Asn Ala His Gly Phe Ile Ser Gly Leu
                1125                1130                1135
Pro Glu Gly Tyr Lys Thr Pro Val Gly Glu Arg Gly Val Gln Leu Ser
            1140                1145                1150
Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Val Leu Lys Asn
        1155                1160                1165
Pro Thr Val Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu
    1170                1175                1180
Ser Glu Cys Val Leu Gln Glu Ala Leu Glu Arg Leu Met Arg Gly Arg
1185                1190                1195                1200
Thr Thr Val Val Val Ala His Arg Leu Ser Thr Ile Arg Gly Val Asp
                1205                1210                1215
Cys Ile Gly Val Ile Gln Asp Gly Arg Ile Val Glu Gln Gly Ser His
            1220                1225                1230
Ser Glu Leu Val Ser Arg Pro Glu Gly Ala Tyr Ser Arg Leu Leu Gln
        1235                1240                1245
Leu Gln Thr His Arg Ile
    1250
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<300>
<308> Genbank P08183
<309> 1997-11-01

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Phe Lys Leu Asn Asn Lys Ser Glu Lys Asp Lys Lys Glu Lys Lys Pro
            20                  25                  30
Thr Val Ser Val Phe Ser Met Phe Arg Tyr Ser Asn Trp Leu Asp Lys
        35                  40                  45
Leu Tyr Met Val Val Gly Thr Leu Ala Ala Ile Ile His Gly Ala Gly
    50                  55                  60
Leu Pro Leu Met Met Leu Val Phe Gly Glu Met Thr Asp Ile Phe Ala
65                  70                  75                  80
Asn Ala Gly Asn Leu Glu Asp Leu Met Ser Asn Ile Thr Asn Arg Ser
                85                  90                  95
Asp Ile Asn Asp Thr Gly Phe Phe Met Asn Leu Glu Glu Asp Met Thr
            100                 105                 110
Arg Tyr Ala Tyr Tyr Tyr Ser Gly Ile Gly Ala Gly Val Leu Val Ala
        115                 120                 125
Ala Tyr Ile Gln Val Ser Phe Trp Cys Leu Ala Ala Gly Arg Gln Ile
    130                 135                 140
His Lys Ile Arg Lys Gln Phe Phe His Ala Ile Met Arg Gln Glu Ile
145                 150                 155                 160
Gly Trp Phe Asp Val His Asp Val Gly Glu Leu Asn Thr Arg Leu Thr
                165                 170                 175
Asp Asp Val Ser Lys Ile Asn Glu Val Ile Gly Asp Lys Ile Gly Met
            180                 185                 190
Phe Phe Gln Ser Met Ala Thr Phe Phe Thr Gly Phe Ile Val Gly Phe
        195                 200                 205
Thr Arg Gly Trp Lys Leu Thr Leu Val Ile Leu Ala Ile Ser Pro Val
    210                 215                 220
Leu Gly Leu Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ser Phe Thr
225                 230                 235                 240
Asp Lys Glu Leu Leu Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu
                245                 250                 255
```

```
Val Leu Ala Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Lys Lys
            260                 265                 270
Glu Leu Glu Arg Tyr Asn Lys Asn Leu Glu Glu Ala Lys Arg Ile Gly
        275                 280                 285
Ile Lys Lys Ala Ile Thr Ala Asn Ile Ser Ile Gly Ala Ala Phe Leu
    290                 295                 300
Leu Ile Tyr Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Thr Thr Leu
305                 310                 315                 320
Val Leu Ser Gly Glu Tyr Ser Ile Gly Gln Val Leu Thr Val Phe Phe
                325                 330                 335
Ser Val Leu Ile Gly Ala Phe Ser Val Gly Gln Ala Ser Pro Ser Ile
            340                 345                 350
Glu Ala Phe Ala Asn Ala Arg Gly Ala Ala Tyr Glu Ile Phe Lys Ile
        355                 360                 365
Ile Asp Asn Lys Pro Ser Ile Asp Ser Tyr Ser Lys Ser Gly His Lys
    370                 375                 380
Pro Asp Asn Ile Lys Gly Asn Leu Glu Phe Arg Asn Val His Phe Ser
385                 390                 395                 400
Tyr Pro Ser Arg Lys Glu Val Lys Ile Leu Lys Gly Leu Asn Leu Lys
                405                 410                 415
Val Gln Ser Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly
            420                 425                 430
Lys Ser Thr Thr Val Gln Leu Met Gln Arg Leu Tyr Asp Pro Thr Glu
        435                 440                 445
Gly Met Val Ser Val Asp Gly Gln Asp Ile Arg Thr Ile Asn Val Arg
    450                 455                 460
Phe Leu Arg Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe
465                 470                 475                 480
Ala Thr Thr Ile Ala Glu Asn Ile Arg Tyr Gly Arg Glu Asn Val Thr
                485                 490                 495
Met Asp Glu Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe
            500                 505                 510
Ile Met Lys Leu Pro His Lys Phe Asp Thr Leu Val Gly Glu Arg Gly
        515                 520                 525
Ala Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala
    530                 535                 540
Leu Val Arg Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala
545                 550                 555                 560
Leu Asp Thr Glu Ser Glu Ala Val Val Gln Val Ala Leu Asp Lys Ala
                565                 570                 575
Arg Lys Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Val
            580                 585                 590
Arg Asn Ala Asp Val Ile Ala Gly Phe Asp Asp Gly Val Ile Val Glu
        595                 600                 605
Lys Gly Asn His Asp Glu Leu Met Lys Glu Lys Gly Ile Tyr Phe Lys
    610                 615                 620
Leu Val Thr Met Gln Thr Ala Gly Asn Glu Val Glu Leu Glu Asn Ala
625                 630                 635                 640
Ala Asp Glu Ser Lys Ser Glu Ile Asp Ala Leu Glu Met Ser Ser Asn
                645                 650                 655
Asp Ser Arg Ser Ser Leu Ile Arg Lys Arg Ser Thr Arg Arg Ser Val
            660                 665                 670
Arg Gly Ser Gln Ala Gln Asp Arg Lys Leu Ser Thr Lys Glu Ala Leu
        675                 680                 685
Asp Glu Ser Ile Pro Pro Val Ser Phe Trp Arg Ile Met Lys Leu Asn
    690                 695                 700
Leu Thr Glu Trp Pro Tyr Phe Val Val Gly Val Phe Cys Ala Ile Ile
705                 710                 715                 720
Asn Gly Gly Leu Gln Pro Ala Phe Ala Ile Ile Phe Ser Lys Ile Ile
                725                 730                 735
Gly Val Phe Thr Arg Ile Asp Asp Pro Glu Thr Lys Arg Gln Asn Ser
            740                 745                 750
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Asn Leu Phe Ser Leu Leu Phe Leu Ala Leu Gly Ile Ile Ser Phe Ile
        755                 760                 765
Thr Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu
    770                 775                 780
Thr Lys Arg Leu Arg Tyr Met Val Phe Arg Ser Met Leu Arg Gln Asp
785                 790                 795                 800
Val Ser Trp Phe Asp Asp Pro Lys Asn Thr Thr Gly Ala Leu Thr Thr
                805                 810                 815
Arg Leu Ala Asn Asp Ala Ala Gln Val Lys Gly Ala Ile Gly Ser Arg
            820                 825                 830
Leu Ala Val Ile Thr Gln Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile
        835                 840                 845
Ile Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Leu Ala Ile
    850                 855                 860
Val Pro Ile Ile Ala Ile Ala Gly Val Val Glu Met Lys Met Leu Ser
865                 870                 875                 880
Gly Gln Ala Leu Lys Asp Lys Lys Glu Leu Glu Gly Ala Gly Lys Ile
                885                 890                 895
Ala Thr Glu Ala Ile Glu Asn Phe Arg Thr Val Val Ser Leu Thr Gln
            900                 905                 910
Glu Gln Lys Phe Glu His Met Tyr Ala Gln Ser Leu Gln Val Pro Tyr
        915                 920                 925
Arg Asn Ser Leu Arg Lys Ala His Ile Phe Gly Ile Thr Phe Ser Phe
    930                 935                 940
Thr Gln Ala Met Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly
945                 950                 955                 960
Ala Tyr Leu Val Ala His Lys Leu Met Ser Phe Glu Asp Val Leu Leu
                965                 970                 975
Val Phe Ser Ala Val Val Phe Gly Ala Met Ala Val Gly Gln Val Ser
            980                 985                 990
Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Ile Ser Ala Ala His Ile
        995                 1000                1005
Ile Met Ile Ile Glu Lys Thr Pro Leu Ile Asp Ser Tyr Ser Thr Glu
    1010                1015                1020
Gly Leu Met Pro Asn Thr Leu Glu Gly Asn Val Thr Phe Gly Glu Val
1025                1030                1035                1040
Val Phe Asn Tyr Pro Thr Arg Pro Asp Ile Pro Val Leu Gln Gly Leu
                1045                1050                1055
Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly Ser Ser
            1060                1065                1070
Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe Tyr Asp
        1075                1080                1085
Pro Leu Ala Gly Lys Val Leu Leu Asp Gly Lys Glu Ile Lys Arg Leu
    1090                1095                1100
Asn Val Gln Trp Leu Arg Ala His Leu Gly Ile Val Ser Gln Glu Pro
1105                1110                1115                1120
Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn
                1125                1130                1135
Ser Arg Val Val Ser Gln Glu Glu Ile Val Arg Ala Ala Lys Glu Ala
            1140                1145                1150
Asn Ile His Ala Phe Ile Glu Ser Leu Pro Asn Lys Tyr Ser Thr Lys
        1155                1160                1165
Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile
    1170                1175                1180
Ala Ile Ala Arg Ala Leu Val Arg Gln Pro His Ile Leu Leu Leu Asp
1185                1190                1195                1200
Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val Gln Glu
                1205                1210                1215
Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile Ala His
            1220                1225                1230
Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Phe Gln Asn
        1235                1240                1245
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Gly Arg Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala Gln Lys
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Gly Ile Tyr Phe Ser Met Val Ser Val Gln Ala Gly Thr Lys Arg Gln
1265 1270 1275 1280

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<309> 1998-07-15

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Thr Gly Ile Gly Ala Gly Val Leu Ile Val Ala Tyr Ile Gln Val Ser
20 25 30
Leu Trp Cys Leu Ala Ala Gly Arg Gln Ile His Lys Ile Arg Gln Lys
35 40 45
Phe Phe His Ala Ile Met Asn Gln Glu Ile Gly Trp Phe Asp Val His
50 55 60
Asp Val Gly Glu Leu Asn Thr Arg Leu Thr Asp Asp Val Ser Lys Ile
65 70 75 80
Asn Asp Gly Ile Gly Asp Lys Ile Gly Met Phe Phe Gln Ser Ile Thr
85 90 95
Thr Phe Leu Ala Gly Phe Ile Ile Gly Phe Ile Ser Gly Trp Lys Leu
100 105 110
Thr Leu Val Ile Leu Ala Val Ser Pro Leu Ile Gly Leu Ser Ser Ala
115 120 125
Leu Trp Ala Lys Val Leu Thr Ser Phe Thr Asn Lys Glu Leu Gln Ala
130 135 140
Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu Val Leu Ala Ala Ile Arg
145 150 155 160
Thr Val Ile Ala Phe Gly Gly Gln Gln Lys Glu Leu Glu Arg Tyr Asn
165 170 175
Lys Asn Leu Glu Glu Ala Lys Asn Val Gly Ile Lys Lys Ala Ile Thr
180 185 190
Ala Ser Ile Ser Ile Gly Ile Ala Tyr Leu Leu Val Tyr Ala Ser Tyr
195 200 205
Ala Leu Ala Phe Trp Tyr Gly Thr Ser Leu Val Leu Ser Asn Glu Tyr
210 215 220
Ser Ile Gly Glu Val Leu Thr Val Phe Phe Ser Ile Leu Leu Gly Thr
225 230 235 240
Phe Ser Ile Gly His Leu Ala Pro Asn Ile Glu Ala Phe Ala Asn Ala
245 250 255
Arg Gly Ala Ala Phe Glu Ile Phe Lys Ile Ile Asp Asn Glu Pro Ser
260 265 270
Ile Asp Ser Phe Ser Thr Lys Gly Tyr Lys Pro Asp Ser Ile Met Gly
275 280 285
Asn Leu Glu Phe Lys Asn Val His Phe Asn Tyr Pro Ser Arg Ser Glu
290 295 300
Val Gln Ile Leu Lys Gly Leu Asn Leu Lys Val Lys Ser Gly Gln Thr
305 310 315 320
Val Ala Leu Val Gly Asn Ser Gly Cys Gly Lys Ser Thr Thr Val Gln
325 330 335
Leu Met Gln Arg Leu Tyr Asp Pro Leu Glu Gly Val Val Ser Ile Asp
340 345 350
Gly Gln Asp Ile Arg Thr Ile Asn Val Arg Tyr Leu Arg Glu Ile Ile
355 360 365
Gly Val Val Ser Gln Glu Pro Val Leu Phe Ala Thr Thr Ile Ala Glu

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    370                 375                 380
Asn Ile Arg Tyr Gly Arg Glu Asp Val Thr Met Asp Glu Ile Glu Lys
385                 390                 395                 400
Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe Ile Met Lys Leu Pro His
                405                 410                 415
Gln Phe Asp Thr Leu Val Gly Glu Arg Gly Ala Gln Leu Ser Gly Gly
            420                 425                 430
Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg Asn Pro Lys
        435                 440                 445
Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu
    450                 455                 460
Ala Val Val Gln Ala Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Thr
465                 470                 475                 480
Ile Val Ile Ala His Arg Leu Ser Thr Val Arg Asn Ala Asp Val Ile
                485                 490                 495
Ala Gly Phe Asp Gly Gly Val Ile Val Glu Gln Gly Asn His Asp Glu
            500                 505                 510
Leu Met Arg Glu Lys Gly Ile Tyr Phe Lys Leu Val Met Thr Gln Thr
        515                 520                 525
Arg Gly Asn Glu Ile Glu Pro Gly Asn Asn Ala Tyr Gly Ser Gln Ser
    530                 535                 540
Asp Thr Asp Ala Ser Glu Leu Thr Ser Glu Glu Ser Lys Ser Pro Leu
545                 550                 555                 560
Ile Arg Arg Ser Ile Tyr Arg Ser Val His Arg Lys Gln Asp Gln Glu
                565                 570                 575
Arg Arg Leu Ser Met Lys Glu Ala Val Asp Glu Asp Val Pro Leu Val
            580                 585                 590
Ser Phe Trp Arg Ile Leu Asn Leu Asn Leu Ser Glu Trp Pro Tyr Leu
        595                 600                 605
Leu Val Gly Val Leu Cys Ala Val Ile Asn Gly Cys Ile Gln Pro Val
    610                 615                 620
Phe Ala Ile Val Phe Ser Arg Ile Val Gly Val Phe Ser Arg Asp Asp
625                 630                 635                 640
Asp His Glu Thr Lys Arg Gln Asn Cys Asn Leu Phe Ser Leu Phe Phe
                645                 650                 655
Leu Val Met Gly Leu Ile Ser Phe Val Thr Tyr Phe Phe Gln Gly Phe
            660                 665                 670
Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr Lys Arg Val Arg Tyr Met
        675                 680                 685
Val Phe Lys Ser Met Leu Arg Gln Asp Ile Ser Trp Phe Asp Asp His
    690                 695                 700
Lys Asn Ser Thr Gly Ser Leu Thr Thr Arg Leu Ala Ser Asp Ala Ser
705                 710                 715                 720
Ser Val Lys Gly Ala Met Gly Ala Arg Leu Ala Val Val Thr Gln Asn
                725                 730                 735
Val Ala Asn Leu Gly Thr Gly Val Ile Leu Ser Leu Val Tyr Gly Trp
            740                 745                 750
Gln Leu Thr Leu Leu Leu Val Val Ile Ile Pro Leu Ile Val Leu Gly
        755                 760                 765
Gly Ile Ile Glu Met Lys Leu Leu Ser Gly Gln Ala Leu Lys Asp Lys
    770                 775                 780
Lys Gln Leu Glu Ile Ser Gly Lys Ile Ala Thr Glu Ala Ile Glu Asn
785                 790                 795                 800
Phe Arg Thr Ile Val Ser Leu Thr Arg Glu Gln Lys Phe Glu Thr Met
                805                 810                 815
Tyr Ala Gln Ser Leu Gln Val Pro Tyr Arg Asn Ala Met Lys Lys Ala
            820                 825                 830
His Val Phe Gly Ile Thr Phe Ser Phe Thr Gln Ala Met Met Tyr Phe
        835                 840                 845
Ser Tyr Ala Ala Cys Phe Arg Phe Gly Ala Tyr Leu Val Ala Gln Gln
    850                 855                 860
Leu Met Thr Phe Glu Asn Val Met Leu Val Phe Ser Ala Val Val Phe
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865                 870                 875                 880
Gly Ala Met Ala Ala Gly Asn Thr Ser Ser Phe Ala Pro Asp Tyr Ala
                885                 890                 895
Lys Ala Lys Val Ser Ala Ser His Ile Ile Arg Ile Ile Glu Lys Thr
            900                 905                 910
Pro Glu Ile Asp Ser Tyr Ser Thr Glu Gly Leu Lys Pro Thr Leu Leu
        915                 920                 925
Glu Gly Asn Val Lys Phe Asn Gly Val Gln Phe Asn Tyr Pro Thr Arg
    930                 935                 940
Pro Asn Ile Pro Val Leu Gln Gly Leu Ser Leu Glu Val Lys Lys Gly
945                 950                 955                 960
Gln Thr Leu Ala Leu Val Gly Ser Ser Gly Cys Gly Lys Ser Thr Val
                965                 970                 975
Val Gln Leu Leu Glu Arg Phe Tyr Asp Pro Met Ala Gly Ser Val Phe
            980                 985                 990
Leu Asp Gly Lys Glu Ile Lys Gln Leu Asn Val Gln Trp Leu Arg Ala
        995                 1000                1005
His Leu Gly Ile Val Ser Gln Glu Pro Ile Leu Phe Asp Cys Ser Ile
    1010                1015                1020
Ala Glu Asn Ile Ala Tyr Gly Asp Asn Ser Arg Ala Val Ser His Glu
1025                1030                1035                1040
Glu Ile Val Arg Ala Ala Lys Glu Ala Asn Ile His Gln Phe Ile Asp
                1045                1050                1055
Ser Leu Pro Asp Lys Tyr Asn Thr Arg Val Gly Asp Lys Gly Thr Gln
            1060                1065                1070
Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val
        1075                1080                1085
Arg Gln Pro His Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp
    1090                1095                1100
Thr Glu Ser Glu Lys Val Val Gln Glu Ala Leu Asp Lys Ala Arg Glu
1105                1110                1115                1120
Gly Arg Thr Cys Ile Val Ile Ala His Arg Leu Ser Thr Ile Gln Asn
                1125                1130                1135
Ala Asp Leu Ile Val Val Ile Glu Asn Gly Lys Val Lys Glu His Gly
            1140                1145                1150
Thr His Gln Gln Leu Leu Ala Gln Lys Gly Ile Tyr Phe Ser Met Val
        1155                1160                1165
Gln Ala Gly Ala Lys Arg Ser
    1170                1175

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      <212> PRT
      <213> Homo sapiens

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      <308> Genbank P21439
      <309> 1998-07-15

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 1               5                  10                  15
Ser Ala Ala Val Trp Ala Lys Ile Leu Ser Ala Phe Ser Asp Lys Glu
            20                  25                  30
Leu Ala Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu Ala Leu Gly
        35                  40                  45
Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Asn Lys Glu Leu Glu
    50                  55                  60
Arg Tyr Gln Lys His Leu Glu Asn Ala Lys Glu Ile Gly Ile Lys Lys
65                  70                  75                  80
Ala Ile Ser Ala Asn Ile Ser Met Gly Ile Ala Phe Leu Leu Ile Tyr
                85                  90                  95
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Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Ser Thr Leu Val Ile Ser
            100                 105                 110
Lys Glu Tyr Thr Ile Gly Asn Ala Met Thr Val Phe Phe Ser Ile Leu
        115                 120                 125
Ile Gly Ala Phe Ser Val Gly Gln Ala Ala Pro Cys Ile Asp Ala Phe
    130                 135                 140
Ala Asn Ala Arg Gly Ala Ala Tyr Val Ile Phe Asp Ile Ile Asp Asn
145                 150                 155                 160
Asn Pro Lys Ile Asp Ser Phe Ser Glu Arg Gly His Lys Pro Asp Ser
                165                 170                 175
Ile Lys Gly Asn Leu Glu Phe Asn Asp Val His Phe Ser Tyr Pro Ser
            180                 185                 190
Arg Ala Asn Val Lys Ile Leu Lys Gly Leu Asn Leu Lys Val Gln Ser
        195                 200                 205
Gly Gln Thr Val Ala Leu Val Gly Ser Ser Gly Cys Gly Lys Ser Thr
    210                 215                 220
Thr Val Gln Leu Ile Gln Arg Leu Tyr Asp Pro Asp Glu Gly Thr Ile
225                 230                 235                 240
Asn Ile Asp Gly Gln Asp Ile Arg Asn Phe Asn Val Asn Tyr Leu Arg
                245                 250                 255
Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe Ser Thr Thr
            260                 265                 270
Ile Ala Glu Asn Ile Cys Tyr Gly Arg Gly Asn Val Thr Met Asp Glu
        275                 280                 285
Ile Lys Lys Ala Val Lys Glu Ala Asn Ala Tyr Glu Phe Ile Met Lys
    290                 295                 300
Leu Pro Gln Lys Phe Asp Thr Leu Val Gly Glu Arg Gly Ala Gln Leu
305                 310                 315                 320
Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg
                325                 330                 335
Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr
            340                 345                 350
Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp Lys Ala Arg Glu Gly
        355                 360                 365
Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Val Arg Asn Ala
    370                 375                 380
Asp Val Ile Ala Gly Phe Glu Asp Gly Val Ile Val Glu Gln Gly Ser
385                 390                 395                 400
His Ser Glu Leu Met Lys Lys Glu Gly Val Tyr Phe Lys Leu Val Asn
                405                 410                 415
Met Gln Thr Ser Gly Ser Gln Ile Gln Ser Glu Glu Phe Glu Leu Asn
            420                 425                 430
Asp Glu Lys Ala Ala Thr Arg Met Ala Pro Asn Gly Trp Lys Ser Arg
        435                 440                 445
Leu Phe Arg His Ser Thr Gln Lys Asn Leu Lys Asn Ser Gln Met Cys
    450                 455                 460
Gln Lys Ser Leu Asp Val Glu Thr Asp Gly Leu Glu Ala Asn Val Pro
465                 470                 475                 480
Pro Val Ser Phe Leu Lys Val Leu Lys Leu Asn Lys Thr Glu Trp Pro
                485                 490                 495
Tyr Phe Val Val Gly Thr Val Cys Ala Ile Ala Asn Gly Gly Leu Gln
            500                 505                 510
Pro Ala Phe Ser Val Ile Phe Ser Glu Ile Ile Ala Ile Phe Gly Pro
        515                 520                 525
Gly Asp Asp Ala Val Lys Gln Gln Lys Cys Asn Ile Phe Ser Leu Ile
    530                 535                 540
Phe Leu Phe Leu Gly Ile Ile Ser Phe Phe Thr Phe Phe Leu Gln Gly
545                 550                 555                 560
Phe Thr Phe Gly Lys Ala Gly Glu Ile Leu Thr Arg Arg Leu Arg Ser
                565                 570                 575
Met Ala Phe Lys Ala Met Leu Arg Gln Asp Met Ser Trp Phe Asp Asp
            580                 585                 590
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His Lys Asn Ser Thr Gly Ala Leu Ser Thr Arg Leu Ala Thr Asp Ala
        595                 600                 605
Ala Gln Val Gln Gly Ala Thr Gly Thr Arg Leu Ala Leu Ile Ala Gln
    610                 615                 620
Asn Ile Ala Asn Leu Gly Thr Gly Ile Ile Ile Ser Phe Ile Tyr Gly
625                 630                 635                 640
Trp Gln Leu Thr Leu Leu Leu Leu Ala Val Val Pro Ile Ile Ala Val
                645                 650                 655
Ser Gly Ile Val Glu Met Lys Leu Leu Ala Gly Asn Ala Lys Arg Asp
            660                 665                 670
Lys Lys Glu Leu Glu Ala Ala Gly Lys Ile Ala Thr Glu Ala Ile Glu
        675                 680                 685
Asn Ile Arg Thr Val Val Ser Leu Thr Gln Glu Arg Lys Phe Glu Ser
    690                 695                 700
Met Tyr Val Glu Lys Leu Tyr Gly Pro Tyr Arg Asn Ser Val Gln Lys
705                 710                 715                 720
Ala His Ile Tyr Gly Ile Thr Phe Ser Ile Ser Gln Ala Phe Met Tyr
                725                 730                 735
Phe Ser Tyr Ala Gly Cys Phe Arg Phe Gly Ala Tyr Leu Ile Val Asn
            740                 745                 750
Gly His Met Arg Phe Arg Asp Val Ile Leu Val Phe Ser Ala Ile Val
        755                 760                 765
Phe Gly Ala Val Ala Leu Gly His Ala Ser Ser Phe Ala Pro Asp Tyr
    770                 775                 780
Ala Lys Ala Lys Leu Ser Ala Ala His Leu Phe Met Leu Phe Glu Arg
785                 790                 795                 800
Gln Pro Leu Ile Asp Ser Tyr Ser Glu Glu Gly Leu Lys Pro Asp Lys
                805                 810                 815
Phe Glu Gly Asn Ile Thr Phe Asn Glu Val Val Phe Asn Tyr Pro Thr
            820                 825                 830
Arg Ala Asn Val Pro Val Leu Gln Gly Leu Ser Leu Glu Val Lys Lys
        835                 840                 845
Gly Gln Thr Leu Ala Leu Val Gly Ser Ser Gly Cys Gly Lys Ser Thr
    850                 855                 860
Val Val Gln Leu Leu Glu Arg Phe Tyr Asp Pro Leu Ala Gly Thr Val
865                 870                 875                 880
Leu Leu Asp Gly Gln Glu Ala Lys Lys Leu Asn Val Gln Trp Leu Arg
                885                 890                 895
Ala Gln Leu Gly Ile Val Ser Gln Glu Pro Ile Leu Phe Asp Cys Ser
            900                 905                 910
Ile Ala Glu Asn Ile Ala Tyr Gly Asp Asn Ser Arg Val Val Ser Gln
        915                 920                 925
Asp Glu Ile Val Ser Ala Ala Lys Ala Ala Asn Ile His Pro Phe Ile
    930                 935                 940
Glu Thr Leu Pro His Lys Tyr Glu Thr Arg Val Gly Asp Lys Gly Thr
945                 950                 955                 960
Gln Leu Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu
                965                 970                 975
Ile Arg Gln Pro Gln Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu
            980                 985                 990
Asp Thr Glu Ser Glu Lys Val Val Gln Glu Ala Leu Asp Lys Ala Arg
        995                 1000                1005
Glu Gly Arg Thr Cys Ile Val Ile Ala His Arg Leu Ser Thr Ile Gln
    1010                1015                1020
Asn Ala Asp Leu Ile Val Val Phe Gln Asn Gly Arg Val Lys Glu His
1025                1030                1035                1040
Gly Thr His Gln Gln Leu Leu Ala Gln Lys Gly Ile Tyr Phe Ser Met
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            20                  25                  30
Leu Ala Ala Tyr Ala Lys Ala Gly Ala Val Ala Glu Glu Ala Pro Gly
        35                  40                  45
Ala Ile Arg Thr Val Ile Ala Phe Gly Gly Gln Asn Lys Glu Leu Glu
    50                  55                  60
Arg Tyr Gln Lys His Leu Glu Asn Ala Lys Lys Ile Gly Ile Lys Lys
65                  70                  75                  80
Ala Ile Ser Ala Asn Ile Ser Met Gly Ile Ala Phe Leu Leu Ile Tyr
                85                  90                  95
Ala Ser Tyr Ala Leu Ala Phe Trp Tyr Gly Ser Thr Leu Val Ile Ser
            100                 105                 110
Lys Glu Tyr Thr Ile Gly Asn Ala Met Thr Val Phe Phe Ser Ile Leu
        115                 120                 125
Ile Gly Ala Phe Ser Val Gly Gln Ala Ala Pro Cys Ile Asp Ala Phe
    130                 135                 140
Ala Asn Ala Arg Gly Ala Ala Tyr Val Ile Phe Asp Ile Ile Asp Asn
145                 150                 155                 160
Asn Pro Lys Ile Asp Ser Phe Ser Glu Arg Gly His Lys Pro Asp Asn
                165                 170                 175
Ile Lys Gly Asn Leu Glu Phe Ser Asp Val His Phe Ser Tyr Pro Ser
            180                 185                 190
Arg Ala Asn Ile Lys Ile Leu Lys Gly Leu Asn Leu Lys Val Lys Ser
        195                 200                 205
Gly Gln Thr Val Ala Leu Val Gly Asn Ser Gly Cys Gly Lys Ser Thr
    210                 215                 220
Thr Val Gln Leu Leu Gln Arg Leu Tyr Asp Pro Thr Glu Gly Lys Ile
225                 230                 235                 240
Ser Ile Asp Gly Gln Asp Ile Arg Asn Phe Asn Val Arg Cys Leu Arg
                245                 250                 255
Glu Ile Ile Gly Val Val Ser Gln Glu Pro Val Leu Phe Ser Thr Thr
            260                 265                 270
Ile Ala Glu Asn Ile Arg Tyr Gly Arg Gly Asn Val Thr Met Asp Glu
        275                 280                 285
Ile Glu Lys Ala Val Lys Glu Ala Asn Ala Tyr Asp Phe Ile Met Lys
    290                 295                 300
Leu Pro Gln Lys Phe Asp Thr Leu Val Gly Asp Arg Gly Ala Gln Leu
305                 310                 315                 320
Ser Gly Gly Gln Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg
                325                 330                 335
Asn Pro Lys Ile Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr
            340                 345                 350
Glu Ser Glu Ala Glu Val Gln Ala Ala Leu Asp Lys Ala Arg Glu Gly
        355                 360                 365
Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr Ile Arg Asn Ala
    370                 375                 380
Asp Val Ile Ala Gly Phe Glu Asp Gly Val Ile Val Glu Gln Gly Ser
385                 390                 395                 400
His Ser Glu Leu Met Lys Lys Glu Gly Ile Tyr Phe Arg Leu Val Asn
                405                 410                 415
Met Gln Thr Ala Gly Ser Gln Ile Leu Ser Glu Glu Phe Glu Ala Arg
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            420                 425                 430
Ala Leu Val Arg Asn Pro Lys Ile Leu Leu Asp Glu Ala Thr Ser
        435                 440                 445
Ala Leu Asp Thr Glu Ser Glu Ala Val Val Gln Val Ala Leu Asp Lys
    450                 455                 460
Ala Arg Lys Gly Arg Thr Thr Ile Val Ile Ala His Arg Leu Ser Thr
465                 470                 475                 480
Val Arg Asn Ala Asp Val Ile Ala Gly Phe Asp Asp Gly Val Ile Val
                485                 490                 495
Glu Lys Gly Asn His Asp Glu Leu Met Lys Glu Lys Gly Ile Tyr Phe
            500                 505                 510
Lys Leu Val Thr Met Gln Thr Ala Gly Asn Glu Val Glu Leu Glu Asn
        515                 520                 525
Ala Ala Ala Arg Ala Leu Val Arg Asn Pro Lys Ile Leu Leu Leu Asp
    530                 535                 540
Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Ala Val Val Gln Ala
545                 550                 555                 560
Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Thr Ile Val Ile Ala His
                565                 570                 575
Arg Leu Ser Thr Val Arg Asn Ala Asp Val Ile Ala Gly Phe Asp Gly
            580                 585                 590
Gly Val Ile Val Glu Gln Gly Asn His Asp Glu Leu Met Arg Glu Lys
        595                 600                 605
Gly Ile Tyr Phe Lys Leu Val Met Thr Gln Thr Arg Gly Asn Glu Ile
    610                 615                 620
Glu Pro Gly Asn Asn Ala Val Glu Leu Ser Asp Glu Lys Ala Ala Gly
625                 630                 635                 640
Asp Val Ala Pro Asn Gly Trp Lys Ala Arg Ile Phe Arg Asn Ser Thr
                645                 650                 655
Lys Lys Ser Leu Lys Ser Pro His Gln Asn Arg Leu Asp Glu Glu Thr
            660                 665                 670
Asn Glu Leu Asp Ala Asn Val Pro Pro Val Ser Phe Leu Lys Val Leu
        675                 680                 685
Lys Leu Asn Lys Thr Glu Trp Pro Tyr Phe Val Val Gly Thr Val Cys
    690                 695                 700
Ala Ile Ala Asn Gly Ala Leu Gln Pro Ala Phe Ser Ile Ile Leu Ser
705                 710                 715                 720
Glu Met Ile Ala Ile Phe Gly Pro Gly Asp Asp Ala Val Lys Gln Gln
                725                 730                 735
Lys Cys Asn Met Phe Ser Leu Val Phe Leu Gly Leu Gly Val Leu Ser
            740                 745                 750
Phe Phe Thr Phe Phe Leu Gln Gly Phe Thr Phe Gly Lys Ala Gly Glu
        755                 760                 765
Ile Leu Thr Thr Arg Leu Arg Ser Met Ala Phe Lys Ala Met Leu Arg
    770                 775                 780
Gln Asp Met Ser Trp Phe Asp Asp His Lys Asn Ser Thr Gly Ala Leu
785                 790                 795                 800
Ser Thr Arg Leu Ala Thr Asp Ala Ala Gln Val Gln Gly Ala Thr Gly
                805                 810                 815
Thr Lys Leu Ala Leu Ile Ala Gln Asn Thr Ala Asn Leu Gly Thr Gly
            820                 825                 830
Ile Ile Ile Ser Phe Ile Tyr Gly Trp Gln Leu Thr Leu Leu Leu Leu
        835                 840                 845
Ser Val Val Pro Phe Ile Ala Val Ala Gly Ile Val Glu Met Lys Met
    850                 855                 860
Leu Ala Gly Asn Ala Lys Arg Asp Lys Lys Glu Met Glu Ala Ala Gly
865                 870                 875                 880
Lys Ile Ala Thr Glu Ala Ile Glu Asn Ile Arg Thr Val Val Ser Leu
                885                 890                 895
Thr Gln Glu Arg Lys Phe Glu Ser Met Tyr Val Glu Lys Leu His Gly
            900                 905                 910
Pro Tyr Arg Asn Ser Val Arg Lys Ala His Ile Tyr Gly Ile Thr Phe
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Ser Ile Ser Gln Ala Phe Met Tyr Phe Ser Tyr Ala Gly Cys Phe Arg
930 935 940
Phe Gly Ser Tyr Leu Ile Val Asn Gly His Met Arg Phe Lys Asp Val
945 950 955 960
Ile Leu Val Phe Ser Ala Ile Val Leu Gly Ala Val Ala Leu Gly His
965 970 975
Ala Ser Ser Phe Ala Pro Asp Tyr Ala Lys Ala Lys Leu Ser Ala Ala
980 985 990
Tyr Leu Phe Ser Leu Phe Glu Arg Gln Pro Leu Ile Asp Ser Tyr Ser
995 1000 1005
Gly Glu Gly Leu Trp Pro Asp Lys Phe Glu Gly Ser Val Thr Phe Asn
1010 1015 1020
Glu Val Val Phe Asn Tyr Pro Thr Arg Ala Asn Val Pro Val Leu Gln
1025 1030 1035 1040
Gly Leu Ser Leu Glu Val Lys Lys Gly Gln Thr Leu Ala Leu Val Gly
1045 1050 1055
Ser Ser Gly Cys Gly Lys Ser Thr Val Val Gln Leu Leu Glu Arg Phe
1060 1065 1070
Tyr Asp Pro Met Ala Gly Ser Val Leu Leu Asp Gly Gln Glu Ala Lys
1075 1080 1085
Lys Leu Asn Val Gln Trp Leu Arg Ala Gln Leu Gly Ile Val Ser Gln
1090 1095 1100
Glu Pro Ile Leu Phe Asp Cys Ser Ile Ala Glu Asn Ile Ala Tyr Gly
1105 1110 1115 1120
Asp Asn Ser Arg Val Val Pro His Asp Glu Ile Val Arg Ala Ala Lys
1125 1130 1135
Glu Ala Asn Ile His Pro Phe Ile Glu Thr Leu Pro Gln Lys Tyr Asn
1140 1145 1150
Thr Arg Val Gly Asp Lys Gly Thr Gln Leu Ser Gly Gly Gln Lys Gln
1155 1160 1165
Arg Ile Ala Ile Ala Arg Ala Leu Ile Arg Gln Pro Arg Val Leu Leu
1170 1175 1180
Leu Asp Glu Ala Thr Ser Ala Leu Asp Thr Glu Ser Glu Lys Val Val
1185 1190 1195 1200
Gln Glu Ala Leu Asp Lys Ala Arg Glu Gly Arg Thr Cys Ile Val Ile
1205 1210 1215
Ala His Arg Leu Ser Thr Ile Gln Asn Ala Asp Leu Ile Val Val Ile
1220 1225 1230
Glu Asn Gly Lys Val Lys Glu His Gly Thr His Gln Gln Leu Leu Ala
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35 40 45

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Glu Ala Ala Leu Asn Gln Asp Ile Gln Phe Phe Asp Thr Glu Val Arg
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Thr Ser Asp Val Val Phe Ala Ile Asn Thr Asp Ala Val Met Val Gln
65                  70                  75                  80
Asp Ala Ile Ser Glu Lys Leu Gly Asn Phe Ile His Tyr Met Ala Thr
                85                  90                  95
Phe Val Ser Gly Phe Ile Val Gly Phe Thr Ala Val Trp Gln Leu Ala
            100                 105                 110
Leu Val Thr Leu Ala Val Val Pro Leu Ile Ala Val Ile Gly Gly Ile
        115                 120                 125
His Thr Thr Thr Leu Ser Lys Leu Ser Asn Lys Ser Gln Glu Ser Leu
    130                 135                 140
Ser Gln Ala Gly Asn Ile Val Glu Gln Thr Val Val Gln Ile Arg Val
145                 150                 155                 160
Val Met Ala Phe Val Gly Glu Ser Arg Ala Ser Gln Ala Tyr Ser Ser
                165                 170                 175
Ala Leu Lys Ile Ala Gln Lys Leu Gly Tyr Lys Thr Gly Leu Ala Lys
            180                 185                 190
Gly Met Gly Leu Gly Ala Thr Tyr Phe Val Val Phe Cys Cys Tyr Ala
        195                 200                 205
Leu Leu Leu Trp Tyr Gly Gly Tyr Leu Val Arg His His Leu Thr Asn
    210                 215                 220
Gly Gly Leu Ala Ile Ala Thr Met Phe Ala Val Met Ile Gly Gly Leu
225                 230                 235                 240
Ala Leu Gly Gln Ser Ala Pro Ser Met Ala Ala Phe Ala Lys Ala Lys
                245                 250                 255
Val Ala Ala Ala Lys Ile Phe Arg Ile Ile Asp His Lys Pro Thr Ile
            260                 265                 270
Glu Arg Asn Ser Glu Ser Gly Val Glu Leu Asp Ser Val Thr Gly Leu
        275                 280                 285
Val Glu Leu Lys Asn Val Asp Phe Ser Tyr Pro Ser Arg Pro Asp Val
    290                 295                 300
Lys Ile Leu Asn Asn Phe Cys Leu Ser Val Pro Ala Gly Lys Thr Ile
305                 310                 315                 320
Ala Leu Val Gly Ser Ser Gly Ser Gly Lys Ser Thr Val Val Ser Leu
                325                 330                 335
Ile Glu Arg Phe Tyr Asp Pro Asn Ser Gly Gln Val Leu Leu Asp Gly
            340                 345                 350
Gln Asp Leu Lys Thr Leu Lys Leu Arg Trp Leu Arg Gln Gln Ile Gly
        355                 360                 365
Leu Val Ser Gln Glu Pro Ala Leu Phe Ala Thr Ser Ile Lys Glu Asn
    370                 375                 380
Ile Leu Leu Gly Arg Pro Asp Ala Asp Gln Val Glu Ile Glu Glu Ala
385                 390                 395                 400
Ala Arg Val Ala Asn Ala His Ser Phe Ile Ile Lys Leu Pro Asp Gly
                405                 410                 415
Phe Asp Thr Gln Val Gly Glu Arg Gly Leu Gln Leu Ser Gly Gly Gln
            420                 425                 430
Lys Gln Arg Ile Ala Ile Ala Arg Ala Met Leu Lys Asn Pro Ala Ile
        435                 440                 445
Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ser Glu Ser Glu Lys
    450                 455                 460
Leu Val Gln Glu Ala Leu Asp Arg Phe Met Ile Gly Arg Thr Thr Leu
465                 470                 475                 480
Ile Ile Ala His Arg Leu Ser Thr Ile Arg Lys Ala Asp Leu Val Ala
                485                 490                 495
Val Leu Gln Gln Gly Ser Val Ser Glu Ile Gly Thr His Asp Glu Leu
            500                 505                 510
Phe Ser Lys Gly Glu Asn Gly Val Tyr Ala Lys Leu Ile Lys Met Gln
        515                 520                 525
Glu Ala Ala His Glu Thr Ala Met Ser Asn Ala Arg Lys Ser Ser Ala
    530                 535                 540
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Arg Pro Ser Ser Ala Arg Asn Ser Val Ser Ser Pro Ile Met Thr Arg
545                 550                 555                 560
Asn Ser Ser Tyr Gly Arg Ser Pro Tyr Ser Arg Arg Leu Ser Asp Phe
                565                 570                 575
Ser Thr Ser Asp Phe Ser Leu Ser Ile Asp Ala Ser Ser Tyr Pro Asn
            580                 585                 590
Tyr Arg Asn Glu Lys Leu Ala Phe Lys Asp Gln Ala Asn Ser Phe Trp
        595                 600                 605
Arg Leu Ala Lys Met Asn Ser Pro Glu Trp Lys Tyr Ala Leu Leu Gly
    610                 615                 620
Ser Val Gly Ser Val Ile Cys Gly Ser Leu Ser Ala Phe Phe Ala Tyr
625                 630                 635                 640
Val Leu Ser Ala Val Leu Ser Val Tyr Tyr Asn Pro Asp His Glu Tyr
                645                 650                 655
Met Ile Lys Gln Ile Asp Lys Tyr Cys Tyr Leu Leu Ile Gly Leu Ser
            660                 665                 670
Ser Ala Ala Leu Val Phe Asn Thr Leu Gln His Ser Phe Trp Asp Ile
        675                 680                 685
Val Gly Glu Asn Leu Thr Lys Arg Val Arg Glu Lys Met Leu Ser Ala
    690                 695                 700
Val Leu Lys Asn Glu Met Ala Trp Phe Asp Gln Glu Glu Asn Glu Ser
705                 710                 715                 720
Ala Arg Ile Ala Ala Arg Leu Ala Leu Asp Ala Asn Asn Val Arg Ser
                725                 730                 735
Ala Ile Gly Asp Arg Ile Ser Val Ile Val Gln Asn Thr Ala Leu Met
            740                 745                 750
Leu Val Ala Cys Thr Ala Gly Phe Val Leu Gln Trp Arg Leu Ala Leu
        755                 760                 765
Val Leu Val Ala Val Phe Pro Val Val Val Ala Ala Thr Val Leu Gln
    770                 775                 780
Lys Met Phe Met Thr Gly Phe Ser Gly Asp Leu Glu Ala Ala His Ala
785                 790                 795                 800
Lys Gly Thr Gln Leu Ala Gly Glu Ala Ile Ala Asn Val Arg Thr Val
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Ala Ala Phe Asn Ser Glu Ala Lys Ile Val Arg Leu Tyr Thr Ala Asn
            820                 825                 830
Leu Glu Pro Pro Leu Lys Arg Cys Phe Trp Lys Gly Gln Ile Ala Gly
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Ser Gly Tyr Gly Val Ala Gln Phe Cys Leu Tyr Ala Ser Tyr Ala Leu
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Gly Leu Trp Tyr Ala Ser Trp Leu Val Lys His Gly Ile Ser Asp Phe
865                 870                 875                 880
Ser Lys Thr Ile Arg Val Phe Met Val Leu Met Val Ser Ala Asn Gly
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        915                 920                 925
Pro Asp Asp Pro Asp Thr Thr Pro Val Pro Asp Arg Leu Arg Gly Glu
    930                 935                 940
Val Glu Leu Lys His Ile Asp Phe Ser Tyr Pro Ser Arg Pro Asp Ile
945                 950                 955                 960
Gln Ile Phe Arg Asp Leu Ser Leu Arg Ala Arg Ala Gly Lys Thr Leu
                965                 970                 975
Ala Leu Val Gly Pro Ser Gly Cys Gly Lys Ser Ser Val Ile Ser Leu
            980                 985                 990
Ile Gln Arg Phe Tyr Glu Pro Ser Ser Gly Arg Val Met Ile Asp Gly
        995                 1000                1005
Lys Asp Ile Arg Lys Tyr Asn Leu Lys Ala Ile Arg Lys His Ile Ala
    1010                1015                1020
Ile Val Pro Gln Glu Pro Cys Leu Phe Gly Thr Thr Ile Tyr Glu Asn
1025                1030                1035                1040
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Ala Thr Leu Ala Ser Ala His Lys Phe Ile Ser Ala Leu Pro Glu Gly
1060 1065 1070
Tyr Lys Thr Tyr Val Gly Glu Arg Gly Val Gln Leu Ser Gly Gly Gln
1075 1080 1085
Lys Gln Arg Ile Ala Ile Ala Arg Ala Leu Val Arg Lys Ala Glu Ile
1090 1095 1100
Met Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Arg
1105 1110 1115 1120
Ser Val Gln Glu Ala Leu Asp Gln Ala Cys Ser Gly Arg Thr Ser Ile
1125 1130 1135
Val Val Ala His Arg Leu Ser Thr Ile Arg Asn Ala His Val Ile Ala
1140 1145 1150
Val Ile Asp Asp Gly Lys Val Ala Glu Gln Gly Ser His Ser His Leu
1155 1160 1165
Leu Lys Asn His Pro Asp Gly Ile Tyr Ala Arg Met Ile Gln Leu Gln
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35 40 45
Arg Ser Met Leu Ser Gln Asp Ile Ser Leu Phe Asp Thr Glu Ala Ser
50 55 60
Thr Gly Glu Val Ile Ser Ala Ile Thr Ser Asp Ile Leu Val Val Gln
65 70 75 80
Asp Ala Leu Ser Glu Lys Val Gly Asn Phe Leu His Tyr Ile Ser Arg
85 90 95
Phe Ile Ala Gly Phe Ala Ile Gly Phe Thr Ser Val Trp Gln Ile Ser
100 105 110
Leu Val Thr Leu Ser Ile Val Pro Leu Ile Ala Leu Ala Gly Gly Ile
115 120 125
Tyr Ala Phe Val Ala Ile Gly Leu Ile Ala Arg Val Arg Lys Ser Tyr
130 135 140
Ile Lys Ala Gly Glu Ile Ala Glu Glu Val Ile Gly Asn Val Arg Thr
145 150 155 160
Val Gln Ala Phe Thr Gly Glu Glu Arg Ala Val Arg Leu Tyr Arg Glu
165 170 175
Ala Leu Glu Asn Thr Tyr Lys Tyr Gly Arg Lys Ala Gly Leu Thr Lys
180 185 190
Gly Leu Gly Leu Gly Ser Met His Cys Val Leu Phe Leu Ser Trp Ala
195 200 205
Leu Leu Val Trp Phe Thr Ser Val Val Val His Lys Asp Ile Ala Asp
210 215 220
Gly Gly Lys Ser Phe Thr Thr Met Leu Asn Val Val Ile Ala Gly Leu

225 230 235 240
Ser Leu Gly Gln Ala Ala Pro Asp Ile Ser Ala Phe Val Arg Ala Lys
245 250 255
Ala Ala Ala Tyr Pro Ile Phe Lys Met Ile Glu Arg Asn Thr Val Thr
260 265 270
Lys Thr Ser Ala Lys Ser Gly Arg Lys Leu Gly Lys Val Asp Gly His
275 280 285
Ile Gln Phe Lys Asp Ala Thr Phe Ser Tyr Pro Ser Arg Pro Asp Val
290 295 300
Val Ile Phe Asp Arg Leu Asn Leu Ala Ile Pro Ala Gly Lys Ile Val
305 310 315 320
Ala Leu Val Gly Gly Ser Gly Ser Gly Lys Ser Thr Val Ile Ser Leu
325 330 335
Ile Glu Arg Phe Tyr Glu Pro Ile Ser Gly Ala Val Leu Leu Asp Gly
340 345 350
Asn Asn Ile Ser Glu Leu Asp Ile Lys Trp Leu Arg Gly Gln Ile Gly
355 360 365
Leu Val Asn Gln Glu Pro Ala Leu Phe Ala Thr Thr Ile Arg Glu Asn
370 375 380
Ile Leu Tyr Gly Lys Asp Asp Ala Thr Ala Glu Glu Ile Thr Arg Ala
385 390 395 400
Ala Lys Leu Ser Glu Ala Ile Ser Phe Ile Asn Asn Leu Pro Glu Gly
405 410 415
Phe Glu Thr Gln Val Gly Glu Arg Gly Ile Gln Leu Ser Gly Gly Gln
420 425 430
Lys Gln Arg Ile Ala Ile Ser Arg Ala Ile Val Lys Asn Pro Ser Ile
435 440 445
Leu Leu Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu Lys
450 455 460
Ser Val Gln Glu Ala Leu Asp Arg Val Met Val Gly Arg Thr Thr Val
465 470 475 480
Val Val Ala His Arg Leu Ser Thr Val Arg Asn Ala Asp Ile Ile Ala
485 490 495
Val Val His Glu Gly Lys Ile Val Glu Phe Gly Asn His Glu Asn Leu
500 505 510
Ile Ser Asn Pro Asp Gly Ala Tyr Ser Ser Leu Leu Arg Leu Gln Glu
515 520 525
Thr Ala Ser Leu Gln Arg Asn Pro Ser Leu Asn Arg Thr Leu Ser Arg
530 535 540
Pro His Ser Ile Lys Tyr Ser Arg Glu Leu Ser Arg Thr Arg Ser Ser
545 550 555 560
Phe Cys Ser Glu Arg Glu Ser Val Thr Arg Pro Asp Gly Ala Asp Pro
565 570 575
Ser Lys Lys Val Lys Val Thr Val Gly Arg Leu Tyr Ser Met Ile Arg
580 585 590
Pro Asp Trp Met Tyr Gly Val Cys Gly Thr Ile Cys Ala Phe Ile Ala
595 600 605
Gly Ser Gln Met Pro Leu Phe Ala Leu Gly Val Ser Gln Ala Leu Val
610 615 620
Ser Tyr Tyr Ser Gly Trp Asp Glu Thr Gln Lys Glu Ile Lys Lys Ile
625 630 635 640
Ala Ile Leu Phe Cys Cys Ala Ser Val Ile Thr Leu Ile Val Tyr Thr
645 650 655
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 800/278, 294, 300; 435/69.1, 71.2, 468, 419, 252.3; 320.1; 536/23.6, 24.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	DUDLER ET AL. Structure of an mdr-like Gene from Arabidopsis thaliana. The Journal of Biological Chemistry. March 1992, Vol. 267, No. 9, pages 5882-5888, see pages 5883, 5885, and 5888.	24, 29-30 ---------- 1-6
Y	CHO et al. An Anion Channel in Arabidopsis Hypocotyls Activited by Blue Light. Proc. Natl. Acad. Sci. USA. July 1996, Vol. 93, pages 8134-8138, see page 8134.	1-2
X --- Y	EMYR DAVIES et al. Cloning and Characterization of a Novel P-Glycoprotein Homologue from Barley . Gene. June 1997, Vol. 199, pages 195-202, see whole document.	24, 29-30 ---------- 1-6

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing data or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 DECEMBER 1999	Date of mailing of the international search report 27 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MEDINA A. IBRAHIM Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ---- Y,P	SIDLER et al. Involvement of an ABC Transporter in a Developmental Pathway Regulating Hypocotyl Cell Elongation in the Light. The Plant Cell. October 1998, Vol. 10, pages 1623-1636, see pages 1623 and 1629-1634.	24, 28-31 ---------- 1-6, 9-23
Y	TOMMASINI et al. Differential Expression of Genes Coding for ABC Transporters after Treatment of Arabidopsis thaliana with Xenobiotics. FEBS Letters. May 1997, Vol. 411, pages 206-210, see page 206.	1-6, 24
A	US 5,786, 162 A (CORBISIER et al) 28 July 1998, see whole document.	1-6, 9-24, 28-31
A	US 5,073,677 A (HELMER et al) 17 December 1991, see whole document.	1-6, 9-24, 28-31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 9-24, 28-31

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/22363

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C12N 5/04, 15/00, 15/09, 15/11, 15/29, 15/63, 15/74, 15/81, 15/82 ; A01H 5/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

800/278, 294, 300; 435/69.1, 71.2, 468, 419, 252.3, 320.1; 536/23.6, 24.1

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

DIALOG, WEST1.2a
SEARCH TERMS: MDR-LIKE GENES, P-GLYCOPROTEIN GENES, ARABIDOPSIS, NPPB, XENOBIOTIC, RESISTANT PLANTS. ABC TRANSPORTER, AtPGP1 EXPRESSION, TRANSGENIC PLANT

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-6, 9-24, 28-31, drawn to an isolated nucleic acid in a recombinant expression cassette, a vector comprising it, a transgenic plant, and a method for producing a plant with enhanced resistance to xenobiotic compounds.
Group II, claim(s) 7-8, 25-26, 32-38, drawn to an isolated protein and antibodies for the protein.
Group III, claim(s) 27, drawn to an oligonucleotide.
Group IV, claim(s) 39-40, drawn to P-glycoprotein gene promoter.
Group V, claim(s) 41-45, drawn to a plant with mutated pIPAC gene and a method of making it.

The inventions listed as Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claimed isolated nucleic acid molecules and transformed cells are anticipated by each of Dudler et al, Emyr Davis et al, and Sidler et al, as set forth in the Search Report, and so do not constitute a single special technical feature which would be an advance over the prior art.

The invention of Group I, drawn to a first product and process of use, requires an isolated nucleic acid encoding P-glycoprotein, a vector, host cells, and a method for plant transformation and regeneration not required by any other group.

The invention of Group II, drawn to a second product, requires an isolated polypeptide and antibodies for the polypeptide not required by any other group.

The invention of Group III, drawn to a third product, requires an oligonucleotide and a hybridization technique not required by any other group.

The invention of Group IV, drawn to a fourth product, requires a specific gene promoter not required by any other group.

The invention of Group V, drawn to a fifth product and method of use, requires a plant with mutated pIPAC gene and a method of making it not required by any other group.